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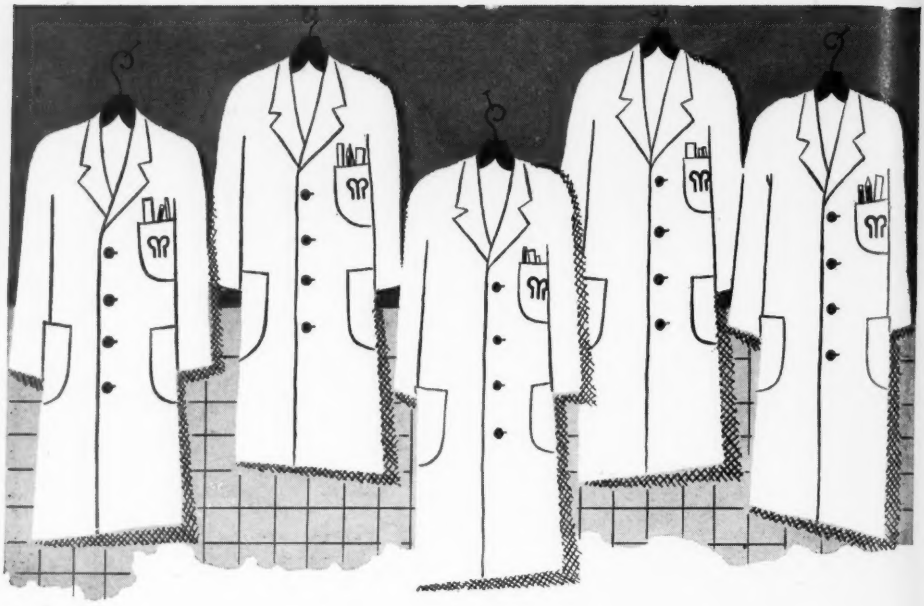

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STUDIES OF THE RELATIONSHIP OF THE THYROTROPIC, EXOPHTHALMIC AND FAT-MOBILIZING PRINCIPLES OF PITUITARY EXTRACT

I. THE EFFECT OF VARIOUS DOSAGES OF PITUITARY EXTRACT UPON THE PRODUCTION OF EXOPHTHALMOS AND THE MOBILIZATION OF FAT IN INTACT AND THYROIDECTOMIZED GUINEA PIGS*§

Van Meter Prize Award Essay

WILLIAM McK. JEFFERIES, M.D.†

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SINCE the studies of Schockaert in 1931 (1) the production of exophthalmos in experimental animals by the injection of pituitary extract has been well established. The principle in pituitary extract responsible for the exophthalmic effect has not been definitely identified, however.

Certain observations suggest a close relationship between this principle and the thyrotropic hormone. In rabbits and guinea pigs thyroidectomy has been reported to have been followed by exophthalmos (2, 3) and to

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* This is the first of three papers reporting work for which *the author received the 1949 Van Meter Prize Award of the American Goiter Association.*

Read at the Annual Meeting of the American Goiter Association, Madison, Wisconsin, May 26, 1949.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1950.

§ The investigation was carried out during the tenure of a fellowship of the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

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enhance the production of exophthalmos by pituitary extract (4, 5, 6) or methyl cyanide (7). Furthermore, pituitary extracts particularly rich in thyrotropic factor have been found to produce experimental exophthalmos (6, 8, 9, 10), whereas preparations of certain other known principles of the anterior and posterior pituitary gland have not (9, 10, 11).

On the other hand, several observations suggest that the thyrotropic and exophthalmic principles of the pituitary are not identical. Pochin (12) maintains that the enhancing effect of thyroidectomy in experimental exophthalmos can be explained by the decreased weight loss experienced by thyroidectomized animals following pituitary injections, and Dobyns (6) found that a supposedly more purified preparation of thyrotropic hormone produced less exophthalmic effect than cruder extracts. The reports of Friedgood (13) and Aird (10) that exophthalmos becomes greatest after animals have become refractory to thyroid-stimulating effect seem incompatible with a theory that these two principles are identical, unless one postulates that refractoriness to one action of the hormone can be developed without refractoriness to the other. Similarly, the findings of Paulson (5) that neither sodium iodide nor diiodotyrosine prevented experimental exophthalmos following pituitary injections, although they did prevent an elevation of basal metabolic rate and lessen the histologic evidence of stimulation of the thyroid, indicate an ability to inhibit thyroid-stimulating effect without apparently affecting the exophthalmos-producing property.

In 1946 (14, 15) Dobyns reported that injections into guinea pigs of pituitary extract containing a fairly high content of thyrotropic hormone produced striking fatty changes in the tissues in addition to the exophthalmic effect. Barrett, Best and Ridout (16) had previously shown that the fatty livers produced by injections of pituitary extract into mice resulted from a mobilization of fat from the body depots. These observations raised the question of a possible relationship between the production of fat-mobilization and the development of exophthalmos.

A series of studies was therefore undertaken in an attempt to throw more light on the relationship of the thyrotropic, exophthalmic and fat-mobilizing effects of pituitary extract. Since a pure preparation of thyrotropic hormone, free from contamination with other pituitary principles, is not available, and since the identity of the factor or factors in pituitary extract responsible for the fatty changes described by Dobyns is not definitely known, the approach to this problem has, of necessity, been rather indirect.

First, a study was made to determine the effect of various dosages of pituitary extract upon the production of exophthalmos and the mobilization of fat in intact versus thyroidectomized guinea pigs. It was designed

to answer the following questions: 1) whether exophthalmic effects and fat deposition in the livers of guinea pigs vary in a comparable fashion with different doses of pituitary extract; 2) whether thyroidectomy enhances the exophthalmic effect or fat deposition at any or all of the dosages; and 3) the smallest doses of pituitary extract which will produce detectable and maximal exophthalmic and fat-mobilizing effects in guinea pigs.

METHOD

This study was performed in two parts. In the first, 23 young guinea pigs were separated into two groups. Eleven were thyroidectomized and the remaining 12 were kept intact. Twelve days later all animals of both groups received the first of two consecutive daily subcutaneous injections. Of the intact guinea pigs, 2 received 2 cc. of normal saline daily as controls, and the remaining 5 pairs received pituitary extract[1] in daily doses of 37.5 mg., 18.75 mg., 7.5 mg., 3.75 mg. and 0.75 mg. respectively. Since 0.75 mg. of this extract contained 1 Junkmann-Schoeller unit of thyrotropic hormone[2,3] these dosages represented 50, 25, 10, 5 and 1 units of thyrotropic hormone (TSH) respectively.[4] The thyroidectomized animals were injected in 6 comparable groups except that only 1 animal received a dose of 37.5 mg. (50 units of TSH). Dilutions of pituitary extract were made from a solution of freshly dissolved dry powder in distilled water in such a manner that the desired dosages were contained in 2 cc. of solution. All animals were males except one and at the time of the first injection all weighed between 195–305 Gm. Their diet consisted of Purina rabbit pellets and lettuce. After the two daily injections all animals were sacrificed with ether on the third day. By this time both exophthalmos (5, 6, 12) and increased fat deposition in the livers (15, 19) should be present. At autopsy, portions of the livers were removed and fixed in 10 per cent aqueous formalin for subsequent frozen sectioning and staining with Scarlach R for fat studies.

Daily measurements of the intercorneal distance (ICD) and body weight

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[1] The pituitary preparation used was a relatively crude powdered extract of a mixture of hog and sheep pituitary glands kindly supplied by the Parke-Davis Company. It contained 1.3 Junkmann-Schoeller units of thyrotropic hormone per milligram of dried powder.

[2] Potency was determined by chick assay according to the method of Albert, *et al.* (17) against a preparation of thyrotropic hormone of known strength. The author is indebted to Mrs. Charlotte Riddell for this determination.

[3] One unit is defined as that amount of extract which, when injected daily for three days into guinea pigs weighing 100 to 150 Gm., causes a recognizable hypertrophy of the thyroid epithelium and disappearance of the colloid in 2 out of 3 animals (18).

[4] Subsequently in this report doses will usually be designated by their thyrotropic content, although obviously other pituitary principles were present in this preparation.

of every guinea pig were made from three days prior to thyroidectomy through the period of injection and again fifteen minutes post mortem. For the purpose of measuring this distance a new instrument was devised which has certain advantages over those previously described in that it is very simple to operate, requires no special placing or bright lighting of the subject animal and is accurate to 0.1 mm. It consists essentially of two pairs of calipers in the form of steel rods, 2 mm. in diameter and pointed

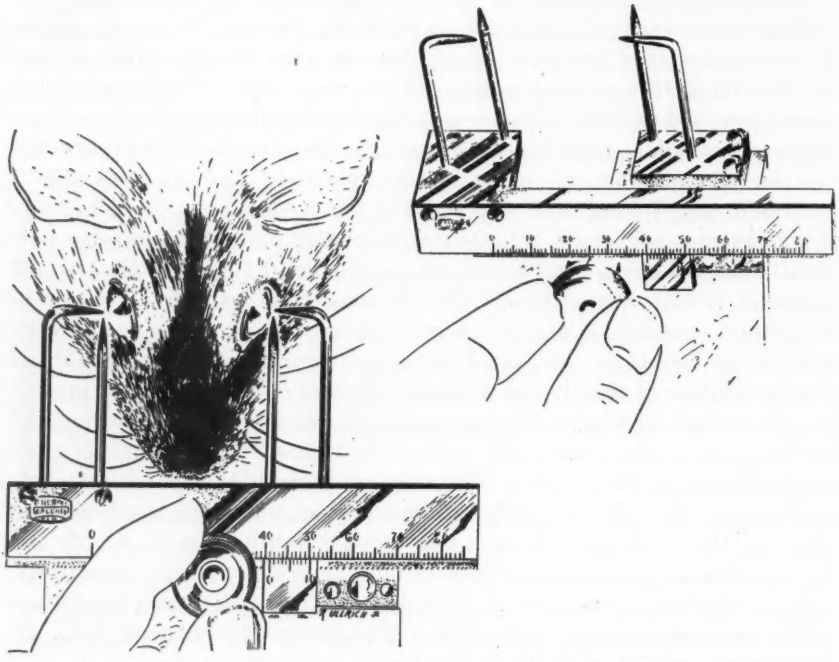

FIG. 1. Instrument for measuring intercorneal distance (ICD) in animals.

at the ends, with a rack and pinion adjustment and a vernier scale (Fig. 1). The calipers are arranged so that one pair is situated above the other, the upper set being more widely spaced than the lower, but bent at right angles near the tips so that their points directly overlie the points of the lower set opposite the respective zero points on the vernier scale. By having two fixed points in a vertical line on the instrument to line up with each of the animal's lateral corneal surfaces an accurate vertical alignment is assured on every measurement without the necessity of the pointers touching or being held very close to the eyes. The lower pointers are usually held 1 or 2 cm. above the lateral corneal surfaces with which they are being aligned. Such an instrument not only can measure accurately to 0.1

mm. the intercorneal distance of any animal whose eyes project laterally from the skull, but it may be easily moved to adjust to varying positions of the animal's head, making it unnecessary to use restraints or have the animal in any special set position.

When performing such measurements on guinea pigs certain precautions should be observed. One must be very careful to avoid alarming stimuli as much as possible. After a loud noise, or if a strong light is shined into its eyes, an animal may retract its globes as much as 1 mm. Even the gentle transfer of an animal from its cage to the table upon which measurements are made may result in retraction of this magnitude, so a delay of two or three minutes after the animal is last handled or alarmed should be made before measuring its intercorneal distance, in order to allow time for the eyes to return to their normal resting state.

Furthermore, as has been noted by Pochin (12) and Dobyns (3, 6) and further confirmed in this laboratory, fluctuations in body weight of experimental animals result in corresponding fluctuations in intercorneal distance. It is therefore desirable to avoid changes in guinea pigs' weights as much as possible in the course of an experiment, and at the same time to follow carefully the body weights in order that proper allowances may be made for any changes which do occur. In order to accomplish the former, several points have been found to be helpful. First, subcutaneous injections of pituitary extract produce less anorexia and resultant interference with food intake than intraperitoneal injections. Presumably the latter may provoke peritoneal irritation. Second, young guinea pigs weighing approximately 200 Gm. experience little if any loss of weight following two daily pituitary injections, whereas older animals frequently lose weight so rapidly that exophthalmos is obscured. Finally, if measurements are made in the morning before the animals are fed, and injections made in the afternoon after the feeding, daily fluctuations in weight due to irregular food intake are kept at a minimum. When changes in body weight do occur, it has been found that, for animals of this size and in the case of weight changes of less than 50 Gm., a correction of the intercorneal distance of 0.1 mm. for each 5 Gm. increase or decrease in weight can be made.[5]

The fat content of the livers as determined histologically was graded from zero to 4+; zero indicating no visible fat in any cells; 1+, occasional scattered cells containing fat; 2+, scattered groups of cells containing fat, which, incidentally, were usually periportal in distribution; 3+, diffuse fatty infiltration involving practically all liver cells; and 4+, a liver in

[5] This correction was determined by following the variations of ICD and body weight of 10 guinea pigs over a period of eleven days, during which time their food and fluid intakes were altered in order to produce changes in body weight.

TABLE 1. THE EFFECT OF VARIOUS DOSAGES OF PITUITARY EXTRACT UPON THE PRODUCTION OF EXOPHTHALMOS AND THE MOBILIZATION OF FAT IN INTACT AND THYROIDECTOMIZED GUINEA PIGS.

GP No.		Injection*	Body weight in grams**	Liver fat (histol'y)	Ante-mortem ICD changes (mm.)‡				Post-mortem ICD changes (mm.)‡		
					Meas.	Time† (hours)	Correction for body weight	Corrected	Meas.	Correction for body weight	Corrected
1	Thyroidectomized	2 cc. normal saline	265	0	+0.7	48	−0.6	+0.1	−0.3	−0.6	−0.9
2	Thyroidectomized	2 cc. normal saline	232	0	+0.6	24	−0.3	+0.3	−0.3	−0.5	−0.8
3	Thyroidectomized	Pit. ext. =50 u TSH	280	2+	+2.0	48	+0.2	+2.2	+1.0	+0.2	+1.2
4	Thyroidectomized	Pit. ext. =25 u TSH	285	2+	+2.8	24	−0.2	+2.6	+2.0	0	+2.0
5	Thyroidectomized	Pit. ext. =25 u TSH	265	2+	+1.3	48	+0.1	+1.4	+1.1	+0.1	+1.2
6	Thyroidectomized	Pit. ext. =10 u TSH	305	2+	+2.6	24	+0.2	+2.8	+0.6	+0.1	+0.7
7	Thyroidectomized	Pit. ext. =10 u TSH	285	3+	+2.5	24	0	+2.5	+1.4	+0.2	+1.6
8	Thyroidectomized	Pit. ext. = 5 u TSH	283	3+	+2.0	24	−0.6	+1.4	+0.6	0	+0.6
9	Thyroidectomized	Pit. ext. = 5 u TSH	296	4+	+1.7	24	−0.2	+1.5	+0.1	+0.1	+0.2
10	Thyroidectomized	Pit. ext. = 1 u TSH	268	1+	+0.5	48	−0.2	+0.3	−0.4	−0.2	−0.6
11	Thyroidectomized	Pit. ext. = 1 u TSH	273	1+	+0.6	24	−0.6	0	−0.2	−0.6	−0.8
12	Intact	2 cc. normal saline	258	0	−0.2	24	−0.3	−0.5	−1.5	−0.6	−2.1
13	Intact	2 cc. normal saline	240	0	+0.3	48	−0.7	−0.4	−1.1	−0.7	−1.8
14	Intact	Pit. ext. =50 u TSH	238	2+	+1.8	24	0	+1.8	+0.7	+0.5	+1.2
15	Intact	Pit. ext. =50 u TSH	287	3+	+2.7	24	0	+2.7	+1.0	+0.5	+1.5
16	Intact	Pit. ext. =25 u TSH	253	4+	+2.9	24	−0.1	+2.8	+1.7	+0.4	+2.1
17	Intact	Pit. ext. =25 u TSH	222	3+	+0.6	48	+0.6	+1.2	−0.8	+0.6	−0.2
18	Intact	Pit. ext. =10 u TSH	239	3+	+1.8	24	−0.2	+1.6	−0.1	+0.2	+0.1
19	Intact	Pit. ext. =10 u TSH	195	2+	+2.9	48	+0.2	+3.1	+0.2	+0.2	+0.4
20	Intact	Pit. ext. = 5 u TSH	240	3+	+1.5	24	0	+1.5	+0.2	+0.3	+0.5
21	Intact	Pit. ext. = 5 u TSH	265	4+	+0.9	48	+0.2	+1.1	−1.4	+0.2	−1.2
22	Intact	Pit. ext. = 1 u TSH	247	0	+0.5	48	−0.3	+0.2	−1.0	−0.3	−1.3
23	Intact	Pit. ext. = 1 u TSH	227	0	+0.7	48	−0.4	+0.3	−1.0	−0.4	−1.4

* Animals received 2 daily subcutaneous injections of the doses indicated, and were sacrificed on the third day.
** At the time of the first injection.
† Time after first injection at which intercorneal distance (ICD) measurement was greatest (hours).
‡ As compared with pre-injection measurements.

which apparently all of the parenchymal cells were loaded with fat. Since the livers of a total of 16 untreated control guinea pigs have been found to contain no more than 1+ fat, the presence of an amount of 2+ or greater is probably indicative of significant fatty infiltration.

In the second portion of the study 10 intact young male guinea pigs weighing 175–250 Gm. were injected in pairs with the same preparation of pituitary extract in daily doses containing 5, 4, 3, 2, and 1 Junkmann-Schoeller units of TSH respectively for two days and sacrificed on the third day. Measurements of intercorneal distance (ICD) and body weight were followed for three days prior to, as well as during, the course of injections and also fifteen minutes post mortem. Pieces of liver were also removed for fat studies as in the first experiment.

RESULTS

No appreciable exophthalmos was noted as a result of thyroidectomy alone. The findings in the first part of the study of the effect of pituitary injections are presented in Table 1. The changes in ICD, both during life and fifteen minutes post mortem, are recorded. The figures in the ante-mortem "measured" column indicate the maximum increase in intercorneal distance following injection as compared with the pre-injection reading, and the post-mortem "measured" column indicates the difference between the reading obtained fifteen minutes after death and the pre-injection measurement. The figures in the "corrected" columns represent the changes in ICD after a correction for changes in body weight which occurred during the intervals under consideration had been made.

Examination of this table reveals several interesting points. It will be noted that the degree of fatty infiltration of the liver did not increase with the size of the dose of pituitary extract above the 5-unit level of TSH. The variations in degree of infiltration above this level may have been due to at least two possibilities. First, larger doses may produce more rapid fat deposition, which is subsiding by the forty-eighth hour. Dobyns (15) noted that guinea pigs injected daily with a preparation of pituitary extract containing 50 Junkmann-Schoeller units of TSH showed an increased deposition of fat in their livers as early as three and one-half hours after the first injection, reaching a maximum at twenty-four hours and slowly diminishing thereafter. Secondly, some of the animals may have had less depot fat available for mobilization. Dible (20) has found that the degree of starvation-induced fatty infiltration of the livers of rats depends upon the quantity of body depot fat available for mobilization at the time fasting was started, so this would probably apply to the fat mobilization following pituitary injections, since the increase in liver fat in both instances has been shown to be derived from body depots (16). Although all of the guinea

pigs were of approximately the same weight at the time this study was started, some gained less rapidly than others so that by the time injections were begun two weeks later, considerable variation of weight was present (*cf.* especially guinea pig #19).

It is also evident that there was no striking difference in fatty infiltration of the livers of the thyroidectomized as compared with the intact animals. This suggests that thyroidectomy does not appreciably affect the fat depo-

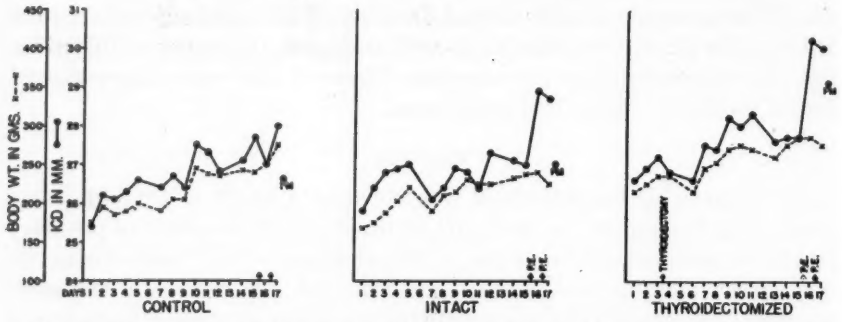

FIG. 2. Exophthalmos in intact and thyroidectomized guinea pigs induced by 2 daily injections of pituitary extract. On the days indicated by the arrows, the control received 2 cc. of normal saline and the other 2 animals received 2 cc. of a freshly prepared solution of pituitary extract containing 10 Junkmann-Schoeller units of thyrotropic activity.

sition in livers of young guinea pigs following injections of pituitary extract.

Figure 2 shows charts of the actual ICD and weight changes of 3 representative animals from these groups and Figure 3 presents a graphic comparison of the exophthalmic effects of the various doses in the intact versus the thyroidectomized guinea pigs. It may be seen that the thyroidectomized animals showed no significant difference from the intact animals in the degree of exophthalmos produced at any dosage level studied. Furthermore, no definite increase in degree of exophthalmos occurred with doses larger than 10 units in either group.

It is also interesting to note from the table that there was very little difference in the weight loss experienced by the intact as compared with the thyroidectomized guinea pigs. This is reflected in the column which shows the corrections made for weight changes, and may be due to the fact that these young guinea pigs experience little if any weight change in the first forty-eight hours after pituitary injections, whereas older animals may lose considerable weight during this period. It may be significant that the only animal which lost more than 10 grams in this experiment (guinea pig #17) was also the only animal injected with a daily dose containing

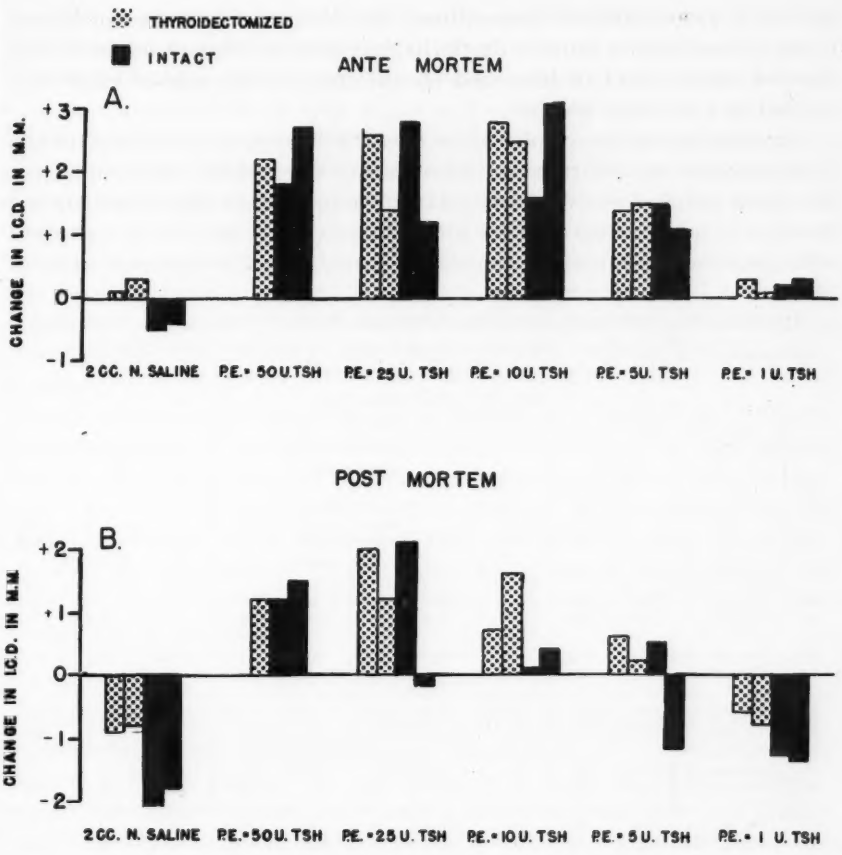

FIG. 3. A comparison of the exophthalmic effects of various doses of pituitary extract in thyroidectomized and intact young guinea pigs.

A. Ante mortem. Maximal increases in ICD measurements following 2 daily subcutaneous injections of the doses indicated.

B. Post mortem. Changes in measurement of ICD made fifteen minutes after death, compared with the pre-injection readings.

10 or more units of TSH which developed less than 1 mm. increase in ICD (uncorrected) and which did not show definite persistence of the exophthalmos post mortem.

When the exophthalmic effect is compared with the fat-mobilizing effect of the various doses it would seem that there is no apparent correlation between the degree of proptosis of the eyes and the degree of fat infiltration in the liver. In fact, the greatest increase in intercorneal distance occurred

in animal #19, one which showed only 2+ fat in the liver. Nevertheless, every animal which showed exophthalmic effect in this experiment also showed some degree of increased fat infiltration and neither effect was present at the 1-unit dosage.

A comparison of the exophthalmic effects persisting post mortem reveals essentially the same correlation and confirms the findings observed during life. Both saline-injected and pituitary-injected guinea pigs experienced a decrease in intercorneal distance fifteen minutes post mortem as compared with measurements made just prior to death, but a comparison of post-

TABLE 2. THE EFFECT OF DOSES OF PITUITARY EXTRACT CONTAINING BETWEEN 1 AND 5 UNITS OF THYROTROPIC ACTIVITY UPON THE PRODUCTION OF EXOPHTHALMOS AND FAT DEPOSITION IN THE LIVER, IN INTACT GUINEA PIGS.

GP No.	Injection*	Body weight in grams**	Liver fat (hist-ol'y)	Ante-mortem ICD changes (mm.)‡				Post-mortem ICD changes (mm.)‡		
				Meas.	Time† (hours)	Correction for body weight	Corrected	Meas.	Corrected for body weight	Corrected
24	Pit. ext. =5 u TSH	208	2+	+1.6	24	−0.2	+1.4	+0.2	+0.1	+0.3
25	Pit. ext. =5 u TSH	194	2+	+2.3	24	−0.1	+2.2	0	+0.3	+0.3
26	Pit. ext. =4 u TSH	223	3+	+2.1	24	−0.2	+1.9	+0.3	+0.2	+0.5
27	Pit. ext. =4 u TSH	176	1+	+0.9	24	−0.2	+0.7	−0.5	0	−0.5
28	Pit. ext. =3 u TSH	175	1+	+1.8	24	−0.3	+1.5	−0.5	+0.1	−0.4
29	Pit. ext. =3 u TSH	222	2+	+1.1	24	0	+1.1	0	+0.2	+0.2
30	Pit. ext. =2 u TSH	234	2+	+0.6	24	−0.2	+0.4	−0.8	0	−0.8
31	Pit. ext. =2 u TSH	215	2+	+0.2	24	+0.1	+0.3	+0.2	+0.1	+0.3
32	Pit. ext. =1 u TSH	201	0	+0.8	48	0	+0.8	0	0	0
33	Pit. ext. =1 u TSH	243	0	+0.1	48	+0.1	+0.2	−0.6	+0.1	−0.5

* Animals received 2 daily subcutaneous injections of the doses indicated, and were sacrificed on the third day.
** At the time of the first injection.
† Time after first injection at which intercorneal distance (ICD) measurement was greatest (hours).
‡ As compared with pre-injection measurements.

mortem readings with pre-injection measurements indicated whether exophthalmos persisted after death.

It will be noted that guinea pigs #17 and #21 did not show persistence of exophthalmos post mortem to a significant degree and these two animals also exhibited a comparatively small exophthalmic effect during life, but their livers showed 3+ and 4+ fat respectively. Hence they strengthen the impression that the degree of fat deposition in the liver following pituitary injections is not necessarily correlated with the degree of exophthalmos produced.

The second portion of this study was undertaken in order to determine

at what dose between the levels of 5 and 1 units of TSH the exophthalmic and fat-mobilizing effects disappeared. The results are presented in Table 2.

It may be seen that histologically demonstrable fatty infiltration of the liver was present with a dosage as low as 2 units, but none occurred at the 1-unit level. Definite exophthalmic effect, however, was not evident below the 3-unit level. The proptosis produced with these smaller doses of pituitary extract was more transient than that produced with larger amounts, reaching a maximum twenty-four hours after the first injection and showing considerable decline at the forty-eight hour measurement. This probably accounts for the finding that post-mortem readings failed to show a consistent correlation with the ante-mortem exophthalmic effect, since exophthalmos was subsiding rather rapidly by the time the animals were sacrificed.

It will be noted that the response of animals #27 and #28 was different from that of the other animals in their respective groups. They both showed slight exophthalmos at the 24-hour measurement, but this subsided rather rapidly so that there was no persistence post mortem, and there was no significant increase in fat in their livers. This behavior may have been related to the fact that both of these guinea pigs were considerably underweight as compared with the other animals in this experiment at the time injections were started.

DISCUSSION

Although the number of animals studied at each dosage level was small, the results were sufficiently clear cut to be informative. Not only did thyroidectomy fail to enhance the production of exophthalmos or the histologically demonstrable mobilization of fat to the liver which occurs within forty-eight hours following pituitary injections in young guinea pigs, but there was no apparent correlation between the degree of exophthalmos and the degree of fatty infiltration of the livers. Nevertheless, the smallest doses of extract which produced detectable effects with regard to these two phenomena were quite close. Hence, although this study indicates that the degree of exophthalmos is not dependent upon the degree of fat mobilization, it does not prove that these two effects are unrelated.

The failure of thyroidectomy to affect the exophthalmos may have been related to the fact that these guinea pigs did not lose weight during the 48-hour period following pituitary injections. In this respect it is interesting to note that the only animal which showed considerable weight loss during the period of injection was the one which showed the smallest degree of exophthalmos when injected with a daily dose containing 10 or more units of TSH. The results of this study are therefore not incompatible with those of Pochin (12), who reported that the enhancing effect of thyroidectomy

on experimental exophthalmos in guinea pigs could be explained by the decreased weight loss experienced by thyroidectomized animals following pituitary injections. It is quite possible that, had daily injections been continued for longer than two days in this experiment, the protection afforded by thyroidectomy against weight loss would have become apparent. In this respect the important point indicated by this study is that thyroidectomy had no appreciable effect on the degree of exophthalmos produced within the first forty-eight hours.

This consideration must also be borne in mind with respect to the dosages found to produce maximal and minimal effects. The findings of this study apply to exophthalmos produced within forty-eight hours of the first daily injection of pituitary extract, but not necessarily to that produced by longer periods of injection. Then, additional factors, such as loss of body weight, development of physiologic adjustments to the effects of pituitary injections and development of antihormone effects, may come into play.

SUMMARY AND CONCLUSIONS

The effect of various doses of pituitary extract upon the production of exophthalmos and the mobilization of fat in intact and thyroidectomized young guinea pigs has been studied. Subcutaneous injections of extract were administered daily for two days and the animals were sacrificed on the third day. Intercorneal distances were measured with a new simple instrument which is accurate to 0.1 mm., and fat mobilization was determined histologically by Scarlach R stains of frozen sections of the livers.

In the first portion of the experiment, daily doses of pituitary extract containing 50, 25, 10, 5 and 1 Junkmann-Schoeller units of thyrotropic hormone were administered, and in the second part daily doses containing 5, 4, 3, 2, and 1 units of TSH were given.

The following results were noted:

1. There was no apparent difference in the degree of proptosis or of fat deposition in the livers produced by comparable doses of pituitary extract in the intact versus thyroidectomized guinea pigs at any of the dosage levels studied. Furthermore, there was no apparent difference in weight changes experienced by either of these groups.

2. Maximal exophthalmic effect occurred with a daily dose of pituitary extract containing 10 or more units of TSH and the smallest dose which produced detectable effect contained 3 units.

3. Maximal fat deposition in the livers occurred with a daily dose of extract containing 5 or more units of TSH and the smallest dose which produced detectable effect contained 2 units.

4. There was no apparent correlation between the degree of exophthalmos and the degree of fat infiltration in the livers in these animals.

It appears, therefore, that thyroidectomy does not enhance either the exophthalmic or the fat-mobilizing effects of two daily injections of pituitary extract in young guinea pigs, and it seems unlikely that the exophthalmic effect is due to the mobilization of fat per se.

Acknowledgment

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STUDIES OF THE RELATIONSHIP OF THE THYROTROPIC, EXOPHTHALMIC AND FAT-MOBILIZING PRINCIPLES OF PITUITARY EXTRACT

II. THE EFFECT OF IODINATION OF PITUITARY EXTRACT UPON THESE THREE PRINCIPLES*§

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Van Meter Prize Award Essay

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IODINATION of preparations of pituitary extract has been found to produce inactivation of the thyroid-stimulating principle by Wright and Trikojus (1) and Albert *et al.* (2). The latter group of investigators (3) also observed that a restoration of most of the thyrotropic potency could be obtained by the addition of thiouracil and certain other reducing agents to the iodinated complex.

Although thyrotropic hormone is not the only physiologic principle which can be inactivated by iodine, since insulin (4), adrenocorticotropic hormone (5) and any other protein hormone in which -SH or tyrosine groups are essential for physiologic activity (6) are apparently susceptible, nevertheless the report by Albert *et al.* that gonadotropic effect persisted in iodinated extract which had lost all thyrotropic activity suggested that it might be possible to inactivate pituitary principles differentially by a suitable technic of iodination. If the thyrotropic factor could be selectively inactivated in this fashion, a study of the effect of the iodinated extract upon the production of exophthalmos and fat infiltration of the liver might indicate whether these two phenomena are dependent upon the presence of thyrotropic activity. Such a study was therefore undertaken.

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Read at the Annual Meeting of the American Goiter Association, Madison, Wisconsin, May 26, 1949.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1950.

§ The investigation was performed during the tenure of a fellowship of the American Cancer Society recommended by the Committee on Growth of the National Research Council.

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METHOD

Two different preparations of pituitary extract were used.[1] Both were rather crude extracts of mixtures of hog and sheep pituitary glands, one being concentrated in a slightly different fashion from the other. The first (P.E. #1) contained 1.3 Junkmann-Schoeller units of thyrotropic activity per milligram of dried powder and the second (P.E. #2) contained 6 units of thyrotropic activity per milligram.[2]

Iodination was carried out with a dilute Lugol's solution containing 10 mg. of iodine per cc. according to the method of Albert *et al.* (2). It was found, however, that when freshly prepared Lugol's solution was used, the iodinated precipitate did not appear until six to eight hours after the pituitary extract was added, whereas with older solutions the precipitate appeared much sooner. This discrepancy turned out to be due chiefly to a difference of acidity, the fresh solutions having a pH of approximately 5.0–6.0, and the older solutions approximately 4.0–4.2. When fresh solutions were adjusted to a pH of 4.2, the precipitate appeared within fifteen minutes. Low temperatures were also found to delay the appearance of the precipitate. Treatment of the iodinated extracts with thiouracil was likewise performed according to the technic of Albert *et al.* (3).

Exophthalmic and fat-mobilizing effects were assayed in young intact male guinea pigs, the extracts being administered subcutaneously in two daily doses containing 10 thyrotropic units in the untreated state, or equivalent amounts of the iodinated and thiouracil-treated material, and the animals sacrificed with ether on the third day. The diet consisted of Purina rabbit pellets and lettuce. Daily measurements of intercorneal distance (ICD) were made for several days prior to as well as during the period of injection and again fifteen minutes post mortem with an instrument and technic described in the preceding report (7). Fatty infiltration of the livers was determined histologically from frozen sections stained with Scarlach R and graded zero to 4+ as described in the previous publication.

Assays of thyrotropic activity were made upon 4 day-old sex-linked cockerels according to the method of Albert and his collaborators (2), aliquots of the material administered to guinea pigs being injected into chicks in groups of 10 in such a manner that each chick received the equivalent of 2 units of thyrotropic hormone in the original preparation over a period of three days, being sacrificed on the fourth day. The thyroids were

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[1] These two preparations were kindly supplied by the Parke-Davis Company.

[2] Potency was determined by chick assay according to the method of Albert *et al.* (2) against a preparation of thyrotropic hormone of known strength. The author is indebted to Mrs. Carlotte Riddell for the assay of extract #1 and to Dr. William L. Money for the assay of extract #2.

then removed, trimmed and weighed on a torsion balance. Gonadotropic activity was estimated from the testicular weights of these chicks.

RESULTS

When iodination was performed at the higher pH at room temperature, not only was thyrotropic activity lost, but exophthalmos and fat deposition in the liver failed to appear and gonadotropic activity was considerably decreased. Furthermore, none of the lost activity of these principles was

TABLE 1. EFFECT OF IODINATION AT pH 4.2 UPON THE THYROTROPIC, EXOPHTHALMIC AND FAT-MOBILIZING PRINCIPLES OF PITUITARY EXTRACT IN INTACT GUINEA PIGS.

GP No.	Injection*	Body weight in grams**	Liver fat (histol'y)	Ante-mortem ICD changes (mm.)‡				Post-mortem ICD changes (mm.) corrected‡	Chick thyroid weights§ (mg.)	Chick testis weights§ (mg.)
				Meas.	Time† (hours)	Correction for body weight	Corrected			
50	2 cc normal saline	225	1+	+0.3	24	−0.3	0.0	−1.1	4.03	14.01
51	2 cc normal saline	224	0	+0.2	48	−0.2	0.0	−1.7		
52¶	Pit-ext. #1=10 u TSH	230	3+	+1.0	24	−0.2	+0.8	—	8.58	38.08
53	Pit-ext. #1=10 u TSH	220	4+	+3.2	48	+0.1	+3.3	+1.2		
54	Pit-ext. #1=10 u TSH	213	4+	+3.2	48	+0.2	+3.4	+1.6		
55	Pit-ext. #1=10 u TSH	217	4+	+1.4	24	+0.3	+1.7	+0.5		
56	Iodo-Pit-ext. #1§§	220	2+	+1.5	24	−0.4	+1.1	−1.1	4.08	29.3
57	Iodo-Pit-ext. #1	220	2+	+1.4	24	−0.5	+0.9	−0.8		
58	Iodo-Pit-ext. #1	217	0	+0.9	24	0	+0.9	−0.7		
59	Iodo-Pit-ext. #1	222	2+	+2.1	24	+0.1	+2.2	+0.1		
60	Iodo-Pit-ext. #1+Thiouracil	210	2+	+1.5	48	0	+1.5	−0.1	5.48	28.0
61	Iodo-Pit-ext. #1+Thiouracil	201	3+	+2.1	24	−0.2	+1.9	+0.3		
62	2 cc normal saline	215	0	+0.8	48	−0.3	+0.5	−2.2	3.72	15.23
63	2 cc normal saline	215	0	+1.0	48	−0.3	+0.7	−0.5		
64	Pit-ext. #2=10 u TSH	231	3+	+0.8	48	+0.5	+1.3	−0.1	7.1	38.04
65	Pit-ext. #2=10 u TSH	241	4+	+1.0	48	+0.2	+1.2	−0.2		
66	Iodo-Pit-ext. #2	247	3+	+1.1	48	0	+1.1	−0.3	4.0	22.6
67	Iodo-Pit-ext. #2	235	3+	+1.0	48	+0.1	+1.1	−0.1		
68	Iodo-Pit-ext. #2	237	3+	+1.5	48	0	+1.5	−1.0		
69	Iodo-Pit-ext. #2	231	3+	+0.7	48	+0.2	+0.9	−0.3		
70	Iodo-Pit-ext. #2+Thiouracil	223	4+	+1.3	24	+0.1	+1.4	+0.4	5.52	25.4
71	Iodo-Pit-ext. #2+Thiouracil	255	4+	+1.4	48	+0.3	+1.7	−0.3		
72	Iodo-Pit-ext. #2+Thiouracil	214	4+	+1.5	48	+0.1	+1.6	+0.2		
73	Iodo-Pit-ext. #2+Thiouracil	237	4+	+1.4	48	+0.1	+1.5	0		

* Animals received 2 daily subcutaneous doses of the amounts indicated, and were sacrificed on the third day.

** At the time of the first injection.

† Time after first injection at which intercorneal distance (ICD) measurement was greatest (hours).

‡ As compared with pre-injection measurements.

§ Each figure represents the average measurement for 10 chicks.

¶ This animal died a few hours after the second injection.

§§ In guinea pigs No. 56 through 61, and 66 through 73, the preparations were administered in daily amounts which had originally contained 10 units of TSH.

restored by thiouracil. Irreversible inactivation had apparently occurred.

The results obtained with extract iodinated at pH 4.2 at room temperature were more interesting. They are shown in Table 1.

It is evident from the column of chick thyroid weights that iodination produced almost complete, if not complete, inactivation of the thyrotropic activity. In order to determine more accurately the extent of inactivation, another group of chicks was injected in such a manner that each chick received a quantity of iodinated material which had originally contained 10 units of thyrotropic activity. Their average thyroid weight (4.87 mg.) was not significantly greater than that of their controls (4.31 mg.). Since Albert

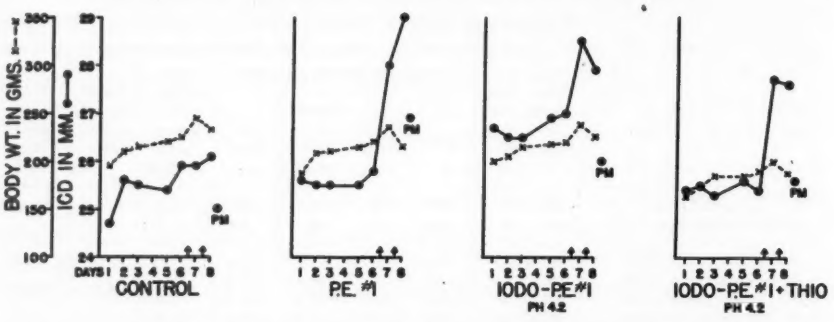

FIG. 1. The exophthalmic effect of iodinated pituitary extract as compared with controls. Charts of representative animals from each group are shown. The control received normal saline and the others received a dose of the preparation indicated, at the times designated by the arrows, in an amount which had originally contained 10 units of thyrotropic activity in the untreated state.

et al. (2) have shown that as little as 0.5 unit of thyrotropic hormone produced an increase in chick thyroid weight with this assay, it follows that the daily dose of iodinated extract injected into guinea pigs contained less than 0.5 unit of thyrotropic activity. It had been found previously (7) that daily doses of extract #1 containing less than 3 units of TSH produced no appreciable exophthalmos, and doses containing less than 2 units produced no fat infiltration of the liver, and similar assays of extract #2 have shown that neither exophthalmos nor fat mobilization occurred with doses containing less than 3 units of TSH. Therefore neither of these effects would be expected in the guinea pigs injected with the iodinated extracts on the basis of any remaining thyrotropic activity which they might contain.

Both exophthalmos and fat infiltration of the livers did occur, however. Although the changes were somewhat less in degree than those produced by untreated extract, they were nevertheless definite (Fig. 1). In Table 2 these effects are compared with the mean of a total of 25 controls, 15 ani-

mals injected with extract #1 and 16 injected with extract #2 in quantities containing 10 units of thyrotropic activity, daily for two days. Statistical analyses of the increases in proptosis, using the "student" formula, indicate a high degree of significance for the exophthalmos produced ante mortem by the iodinated as well as the untreated and the thiouracil-treated extract in comparison with the controls.[3] The post-mortem measurements revealed a considerable decrease of intercorneal distance from the maximum ante-mortem reading in all animals as had been noted in the previous study (7) but when the post-mortem measurements were compared with the pre-

TABLE 2. THE EFFECTS OF IODINATION UPON THE EXOPHTHALMIC AND FAT-MOBILIZING PROPERTIES OF PITUITARY EXTRACT IN INTACT GUINEA PIGS.

Group*	No. of animals	Liver fat (histol'y)	Maximum inc. in ICD (mm.)†	Minimum inc. in ICD (mm.)†	Mean	Standard deviation	Value of p‡
Ante mortem:							
2 cc normal saline	25		+1.1	−0.9	+0.06	0.52	
Pit-ext. #1 = 10 u TSH	15		+3.5	+1.4	+2.3	0.57	<0.001
Iodo-Pit-ext. #1**	4		+2.2	+0.9	+1.28	0.61	<0.001
Iodo-Pit-ext. #1 + Thiouracil**	2		+1.9	+1.5	+1.7	0.28	<0.001
Pit-ext. #2 = 10 u TSH	16		+2.5	+1.2	+2.0	0.46	<0.001
Iodo-Pit-ext. #2**	4		+1.5	+0.9	+1.15	0.48	<0.001
Iodo-Pit-ext. #2 + Thiouracil**	4		+1.7	+1.4	+1.55	0.11	<0.001
Post mortem:							
2 cc normal saline	19	0 −1+	−0.3	−2.6	−1.2	0.67	
Pit-ext. #1 = 10 u TSH	13	3+−4+	+1.6	+0.1	+0.75	0.44	<0.001
Iodo-Pit-ext. #1	4	0 −2+§	+0.1	−1.1	−0.62	0.52	<0.2>0.1
Iodo-Pit-ext. #1 + Thiouracil	2	2+−3+	+0.3	−0.1	+0.1	0.28	<0.02>0.01
Pit-ext. #2 = 10 u TSH	14	3+−4+	+1.4	−0.3	+0.54	0.54	<0.001
Iodo-Pit-ext. #2	4	3+	−0.1	−1.0	−0.43	0.4	<0.05>0.02
Iodo-Pit-ext. #2 + Thiouracil	4	4+	+0.4	−0.3	+0.08	0.3	<0.001

* Indicated doses were administered subcutaneously for two days and the animals sacrificed on the third day.
** These preparations were administered in daily amounts which had originally contained 10 units of TSH.
† As compared with pre-injection measurements and corrected for changes in body weight.
‡ Values less than 0.01 are of statistical significance.
§ One animal's liver showed no fat, the other three, 2+.

injection readings the differences between the pituitary-treated and the control guinea pigs became evident. These post-mortem differences were great enough to be of statistical significance in the groups injected with untreated extract, but not in those which received the iodinated preparations, possibly due to the fact that milder degrees of exophthalmos tend to sub-

[3] Since the preparation of this table, the exophthalmic effect of iodinated extract has been studied in 16 more guinea pigs, making a total of 24 animals in this group. Statistical analysis of the entire group reveals an even greater degree of significance of the exophthalmos produced, the value of t for the entire group being 7.316 as compared with 4.26 and 4.07, respectively, for the two groups of 4 animals which received iodinated extract listed in the table above.

side earlier. In Figure 2 the changes in intercorneal distance have been charted graphically for the sake of comparison.

It appears, therefore, that iodination at pH 4.2 produced over 95 per cent inactivation of the thyrotropic principle, but demonstrable exophthalmic and fat-mobilizing effects persisted. Furthermore, gonadotropic ac-

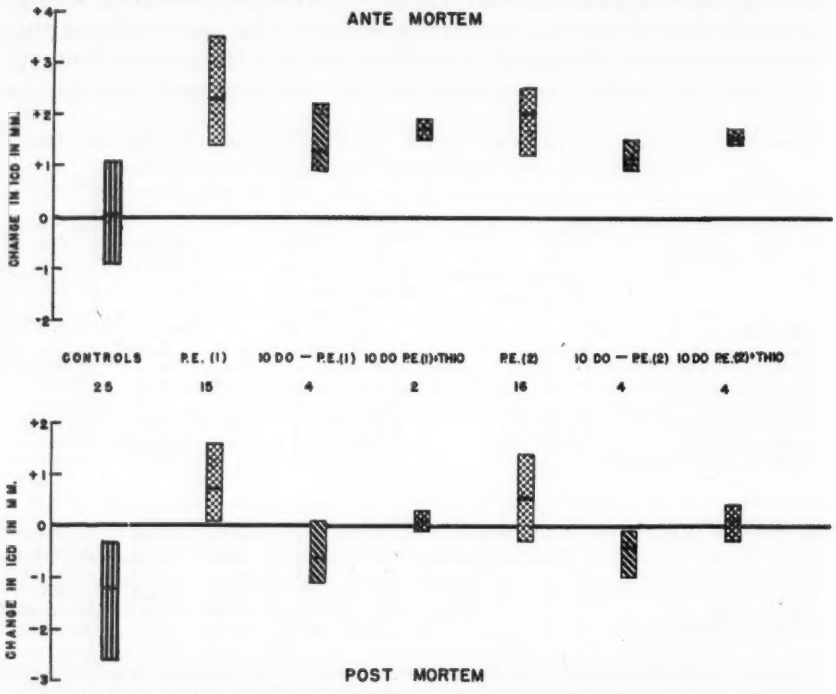

FIG. 2. A comparison of the exophthalmic effects of untreated pituitary extract, of iodinated pituitary extract (at pH 4.2) and of the iodinated extract after treatment with thiouracil in intact young guinea pigs. Each preparation was administered in two daily doses which originally contained 10 units of thyrotropic activity in the untreated state. The number of animals studied in each group is indicated under the type of treatment. The horizontal line through each column represents the mean, and the column itself, the range between the maximum and minimum effects.

tivity, as determined by chick testis weights, was partially decreased by such iodination. Injection of dilute Lugol's solution and pituitary extract at separate subcutaneous sites into both chicks and guinea pigs resulted in no impairment of thyrotropic, exophthalmic, or fat-mobilizing effects during the time required by the respective assays.

Treatment of the iodinated extract with thiouracil resulted in partial restoration of the thyrotropic activity, and probably also of exophthalmic

and fat-mobilizing properties, although the increases in the latter two effects were comparatively slight and hence difficult to evaluate. There was no apparent restoration of gonadotropic activity. Thiouracil alone administered subcutaneously in comparable doses produced no exophthalmos or fat-mobilization in guinea pigs and no increase in chick thyroid weights during the periods required by the assays.

Since these experiments were performed in such a manner that the guinea pig and chick assays were started on the day that the pituitary extract was iodinated, the guinea pigs being injected for two days and sacrificed on the third, and the chicks being injected for three days and sacrificed on the fourth, additional control studies were necessary to determine whether the element of time required by these assays might have influenced the results. Could the iodinated extract have retained sufficient thyrotropic activity (*i.e.* 3 or more units per injection) on the first one or two days after iodination to have been a factor in the production of exophthalmos and fat mobilization in the guinea pigs, but have lost this activity upon standing in the refrigerator to such an extent that the chick assays were negative?

In order to investigate this possibility the following experiment was performed. On the first day a sufficient quantity of pituitary extract #2 was iodinated to treat 4 groups of guinea pigs and 4 groups of chicks in the following manner: *Guinea pigs* (each group consisted of 2 animals, and the daily dose was a quantity of iodinated extract which had originally contained 10 units of TSH): Group 1, injected only on the first day and sacrificed on the second day; Group 2, injected on the first and second day and sacrificed on the third day; Group 3, injected on the third and fourth days and sacrificed on the fifth; and Group 4, injected on the fourth day and sacrificed on the fifth day. *Chicks* (each group consisted of 10 chicks); Group A, controls, injected with 1 cc. of distilled water on days 1–3; Group B, injected with a quantity of pituitary extract #2 containing 2/3 unit of TSH in 1 cc. aqueous solution on days 1–3 (total of 2 units per chick); Group C, injected with iodinated extract in an amount which originally had contained 10/3 units of TSH in 1 cc. solution on days 1–3 (total of 10 units in terms of original activity per chick); Group D, injected with a quantity of untreated pituitary extract containing 3 units of TSH and a quantity of dilute Lugol's solution containing an amount of iodine equivalent to that which would have been expected to combine with the extract in the course of iodination[4] at separate sites on day 1, followed by iodinated extract equivalent to 10/3 units of TSH for days 2 and 3. All chicks were sacrificed on the fourth day.

[4] Albert *et al.* (2) found that a quantity of iodinated extract representing 100 units of TSH contained a total of 4 mg. of iodine.

Thus, if thyrotropic activity were responsible for the exophthalmic and fat-mobilizing effects, and if it were present in sufficient quantities in the iodinated extract on the first day or two following iodination, but not thereafter, Groups 1 and 2 of the guinea pigs should show exophthalmos and fatty livers, but Groups 3 and 4 should not. In addition, the average thyroid weight of the chicks in Group D would not be expected to be any greater than that of those in Group C.

The guinea pigs of Groups 3 and 4 did show definite exophthalmos and fatty livers comparable to the effects shown by Groups 1 and 2, however. Hence the iodinated extract must have lost very little of its exophthalmic and fat-mobilizing activity while being kept in the refrigerator for four days.

Furthermore, the average thyroid weight of chick Group D was definitely higher than that of Group C (Table 3). Hence it is unlikely that the iodinated extract retained considerable thyrotropic activity for the first day after preparation.

TABLE 3. THE EFFECT OF IODINATION OF PITUITARY EXTRACT UPON ITS THYROID-STIMULATING ACTIVITY IN CHICKS.

Group*	Thyroid weight (mg.)
A. Controls (1 cc. distilled water daily)	4.92
B. Pituitary extract #2 (2/3 J-S unit TSH daily)	10.52
C. Iodo-P.E. #2 (10/3 J-S units TSH daily)	6.27
D. P.E. #2 (3 J-S units TSH) +I-KI separately first day, followed by iodo-P.E. (10/3 J-S units TSH) for two days	8.25

* Each group consisted of 10 chicks injected subcutaneously with the indicated doses for three consecutive days and sacrificed on the fourth day.

This experiment also confirms the previous studies, in that a quantity of iodinated extract equivalent to 10 units of original thyrotropic activity (Group C) did not produce as great an increase in thyroid weight as a quantity of untreated extract containing 2 units. The assay consequently indicates that the dose of iodinated extract administered to the guinea pigs contained less than 2 units of thyrotropic activity, a quantity which had been found to be insufficient to produce exophthalmos and fatty infiltration of the liver on the basis of the activity of this principle alone.

DISCUSSION

Although the evidence obtained in these studies is to a great extent indirect, and although the nature of the experiments was such that numerous controls were necessary to evaluate possible extraneous factors, neverthe-

less the results were sufficiently consistent to be reasonably convincing.

Although iodination of pituitary extract at a pH above 5 produced irreversible inactivation of all three principles, iodination at pH 4.2 apparently resulted in less loss of exophthalmic and fat-mobilizing than of thyrotropic activity. Thus, both exophthalmos and fat mobilization were repeatedly produced in guinea pigs by a dose of iodinated extract which contained much less thyrotropic activity by chick assay than was necessary to produce these effects when the untreated extract was administered. Since these effects could not be accounted for on the basis of thyrotropic activity alone, it therefore appears that the role of thyrotropic hormone in experimental exophthalmos is at best an auxiliary one, and the primary factor responsible for the development of this phenomenon remains unidentified. It may be an entirely separate principle of pituitary extract, or it may result from the combined actions of two or more of the recognized principles.

SUMMARY AND CONCLUSIONS

The effect of iodination upon the thyrotropic, exophthalmic and fat-mobilizing principles of pituitary extract has been studied. Thyrotropic activity was assayed in chicks. Exophthalmos and fat mobilization were assayed in young guinea pigs following two daily injections of preparations of pituitary extract. Intercorneal distances were measured with a simple instrument which is accurate to 0.1 mm., and fat mobilization was determined histologically by Scarlach R stains of frozen sections of the livers.

Iodination at pH 5–6 resulted in irreversible inactivation of the thyrotropic, exophthalmic and fat-mobilizing principles. Iodination at pH 4.2 produced up to 95 per cent loss of thyrotropic activity but sufficient exophthalmic and fat-mobilizing activity remained to produce demonstrable effects in young guinea pigs Suitable controls indicated that these effects therefore could not be attributed to the thyrotropic principle alone.

Consequently, the role of thyrotropic hormone in experimental exophthalmos following pituitary injections appears to be at best an auxiliary one, and the primary factor responsible for this phenomenon remains unidentified.

Treatment of the iodinated extract with thiouracil partly restored the thyrotropic activity and apparently slightly increased the exophthalmic and fat-mobilizing effects.

Acknowledgment

The author is indebted to Miss Beatrice Lennon, Miss Priscilla Merrill and Miss Olive Joneson for their technical assistance at various times in the course of these studies.

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STUDIES OF THE RELATIONSHIP OF THE THYROTROPIC, EXOPHTHALMIC AND FAT-MOBILIZING PRINCIPLES OF PITUITARY EXTRACT

III. THE EFFECT OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND DESOXYCORTICOSTERONE ACETATE (DOCA) UPON EXOPHTHALMOS AND FAT MOBILIZATION IN GUINEA PIGS*§

Van Meter Prize Award Essay

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IN the preceding report (1) it has been found that the exophthalmos produced within forty-eight hours by the injection of pituitary extract into guinea pigs cannot be attributed to thyrotropic activity alone. It has also been found that this exophthalmos can hardly be attributed to pituitary-induced mobilization of fat per se (2), since proptosis developed in some animals which showed no increased fat deposition in their livers. Nevertheless, the exophthalmic and fat-mobilizing activity seemed closely related, disappearing approximately together with diminishing doses of pituitary extract and behaving similarly when the extract was iodinated. It therefore seemed advisable to investigate this relationship further, if possible.

Fry (3) has reported that the fatty livers induced by administration of anterior pituitary extract to intact rats cannot be induced in adrenalectomized animals. More recently, Baker *et al.* (4) have noted that the administration of adrenocorticotropic hormone (ACTH) to rats on a high carbohydrate diet has been followed by increased histologic fat in the livers. Consequently, it seemed reasonable to suspect that ACTH might be

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§ The investigation was performed during the tenure of a fellowship of the American Cancer Society recommended by the Committee on Growth of the National Research Council.

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the principle in pituitary extract responsible for the mobilization of fat to the livers of guinea pigs.

Since several previous investigators (5–12) have commented on the edema of the tissues of the orbit of guinea pigs made exophthalmic by pituitary injections, it also seemed possible that the DOCA-like effect of ACTH through its action on the adrenal cortex might be a factor in the production of exophthalmos. Hence the effects of administration of ACTH and of desoxycorticosterone acetate (DOCA) upon the intercorneal distances and fat content of the livers of guinea pigs was studied.

METHOD

Young intact male guinea pigs weighing approximately 200 grams and on a diet of Purina rabbit pellets and lettuce were injected subcutaneously with the desired dosages of ACTH or DOCA for two days and sacrificed on the third day, as in the previous studies with pituitary extract (1, 2). A highly purified preparation of ACTH[1] was administered to 4 animals in doses of 1 mg. daily and to 2 animals in doses of 3 mg. daily. 11-Desoxycorticosterone acetate[2] was administered to 2 animals in doses of 2.5 mg. per day. Daily measurements of intercorneal distance (ICD) and body weight were followed, and at post mortem portions of the livers were fixed in 10 per cent aqueous formalin for subsequent frozen-sectioning and staining with Scarlach R for fat studies as previously described.

RESULTS

None of these animals developed exophthalmos. DOCA produced considerable increase in body weights during the 48-hour period of study, presumably due to fluid retention, but the intercorneal distances did not increase to a greater extent than would have been expected with the change in weight.

One of the guinea pigs which received 1 mg. of ACTH per day had 2+ fat in its liver, but none of the others receiving either ACTH or DOCA showed any histologic fat.

DISCUSSION

In previous studies (1, 2) it has been shown that as little as 2.3 mg. of one preparation of pituitary extract and 0.5 mg. of another would produce both exophthalmos and increased histologic fat in the livers of guinea pigs injected under the conditions of this experiment. Furthermore, a daily dose

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[1] This material was kindly supplied by the Armour Laboratories. Their assays indicated that it contained as contaminants 0.04 unit of oxytocin and 0.04 unit of pitressin per milligram, but thyrotropin and growth hormone were present in negligible quantities.

[2] Percorten (Ciba), 5 mg. per cc. in sesame oil.

of 1–2 mg. of the second preparation consistently produced 3+ to 4+ fatty infiltration of the livers in animals which had normal stores of body fat. Hence the doses of ACTH administered in this experiment should have been sufficient to produce these effects, had they been due entirely to the ACTH content of pituitary extract.

The fact that neither exophthalmos nor increased fat deposition in the livers developed indicates that, if ACTH is a factor in the production of either of these phenomena, it is not the only one. Hence these effects of pituitary extract cannot be attributed to its ACTH content alone.

SUMMARY AND CONCLUSIONS

The effects of administration of adrenocorticotropic hormone (ACTH) and 11-desoxycorticosterone acetate (DOCA) upon the intercorneal distance and histologically demonstrable fat in the livers of young guinea pigs has been studied. No exophthalmos was produced by two daily subcutaneous injections of 1 mg. of ACTH, of 3 mg. of ACTH or of 2.5 mg. of DOCA. Slightly increased fat deposition in the liver was noted in one animal injected with ACTH, but in none of the others.

Since similar doses of pituitary extract have been found to produce both exophthalmos and increased liver fat under the conditions of this experiment, it is unlikely that either ACTH or its DOCA-like effect are solely responsible for the production of either of these effects by pituitary extract.

Acknowledgment

The author is indebted to Miss Beatrice Lennon for technical assistance in this study.

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THE DIRECT ESTIMATION OF THE RATE OF THYROID HORMONE FORMATION IN MAN. THE EFFECT OF THE IODIDE ION ON THYROID IODINE UTILIZATION*

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THE interest of thyroidologists was recently aroused by the demonstration by Wolff and Chaikoff (1) that, with levels of serum iodide higher than 20 to 30 micrograms per cent, organic binding of iodine in the rat thyroid was inhibited. Extension of these observations to man was undertaken in view of the paradox thus presented, *i.e.*, that adequate iodide seemed to prevent hormone formation in the rat and yet failed to control thyrotoxicosis completely or to produce myxedema in man.

Although various indirect methods have been used for estimating the rate of hormone formation in man, such as the amount of thyroid necessary to alleviate myxedema, or the urinary excretion of iodine, no direct measurements of this function have been described.

It is the purpose of this paper to present a method for the direct estimation of the rate of iodine utilization by the thyroid in man, and to determine the effects of various amounts of iodide on this process. A simple method for calculating the serum iodide is also described.

METHODS

The principles utilized were, (a) serial quantitative determinations of radioactive iodine uptake by the thyroid, and (b) calculation of the specific activity of the accumulated thyroid iodine by analysis of the simultaneously excreted urine for both I^{131} and I^{127}.

These procedures are based on the assumption that the two isotopes, I^{131} (radioiodine) and I^{127} (stable iodine), chemically identical in the test tube, are metabolized in exactly the same manner in the body. Then, if the quantity of stable iodine accompanying each microcurie of I^{131} into the

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thyroid is known, the calculation of total iodine accumulation is a simple matter. Since the kidneys excrete the isotopes indiscriminately, there will be the same proportion of each in the serum and in the urine. Or, expressed in another fashion, Serum I^{127}/Serum I^{131} = Urine I^{127}/Urine I^{131}. At any time then, the specific activity (I^{131}/I^{127}) of the iodide in the urine being formed will be the same as that of the serum. Since arterial blood from the same source supplies both the thyroid and the kidneys and contains identical amounts of iodide, the specific activity of the iodide of the urine excreted over a short period will accurately reflect the specific activity of the iodide entering the thyroid during this same period.

A group of 31 euthyroid and 13 untreated thyrotoxic subjects were studied by this method. In all instances a tracer dose of 100 microcuries of I^{131} was administered by mouth. Within a few minutes the subject urinated and discarded the specimen. During the course of the test enough water was drunk to provide an adequate urinary output. At approximately hourly intervals for six to twelve or more hours the radioactivity in the thyroid gland was measured with a sensitive gamma (Geiger-Müller) counter at a distance of 35 centimeters from the gland. The background (radioactivity over the lower thigh just above the knee) was subtracted from the thyroid count. The absolute quantity of I^{131} in microcuries was calculated by comparing the net count with that resulting from a standard radioactive iodine solution under similar geometric conditions. Nearly simultaneously with each thyroid count, urine and blood specimens were collected.

Astwood and Bissell's modification (2) of Kendall's method was used for the analyses of the urines for stable iodine, I^{127}. The I^{131} content of the urine and serum was determined by comparing aliquots evaporated on flamed copper planchets with appropriately diluted portions of the administered I^{131}, using a thin window beta counter. In order to compensate for the greater self-absorption of the serum specimens, appropriate quantities of normal serum (containing no radioactivity) were evaporated on the discs with the urines and standard solutions.

When the successive values representing accumulated I^{131} in the thyroid were plotted against a "square root of time" scale, the parabolic curves were converted to straight lines in normal subjects (3). The effect of inhibiting agents administered during the tests was evident as deviations from this linear course of accumulation. Thus, in normal subjects, antithyroid drugs of various types have been quantitatively assayed by this method (3). In this study, also in euthyroid subjects, the method was utilized in ascertaining the action of the iodide ion. The pattern of iodine collection exhibited by very hyperplastic thyroids such as in thyrotoxicosis could not be fitted to a straight line.

CALCULATIONS

The thyroid accumulation of I^{131} (I^{131} *per hour*): The increase in microcuries for each period was divided by the length of the period. The rate of I^{131} collection was greatest within a short time after administration, and progressively decreased after this. (The calculations of Keating *et al.* (4) indicated that this could be expressed as a "collection rate" which was a constant per cent of the radioactive iodine available to the thyroid. However, since some of our subjects were not observed for a long enough period —twenty-four hours or more—so that the asymptotic levels could be estimated, this expression of the rate of uptake was not calculated for them.)

The specific activity of the urine iodine: This was determined from the fraction, Urine I^{131} (microcuries)/Urine I^{127} (micrograms), which, during the course of the uptake, progressively decreased. In other words, each microcurie of I^{131} collected by the gland represented an increasing quantity of I^{127}.

The rate of thyroid accumulation of I^{127} (I^{127} *per hour*): For each period T equalled I^{131} (microcuries/hour)/Urine specific activity.

Determination of serum iodide (*serum* I^{127}): From the formula Serum I^{127}/Serum I^{131} = Urine I^{127}/Urine I^{131} this value could be readily calculated as Serum I^{127} = Serum $I^{131} \times$ Urine I^{127}/Urine I^{131}. Since the urine values represented *average* levels for the period, it was evident that the mean serum I^{131} level must be calculated from the quantities at the beginning and at the end of the period. The figures obtained for stable iodide (serum I^{127}) obviously also represented average concentrations during the period.

RESULTS

The rates of I^{127} accumulation in 14 euthyroid subjects who had not received additional iodide fell within rather narrow limits, varying from 3 to 19 micrograms/hour, averaging 10 micrograms/hour for periods of from six to twenty-eight hours (Fig. 1). In these individuals the serum iodide levels were in the vicinity of 1 microgram per cent or (usually) less. Although, in general, the amount of I^{127} collected by the thyroid paralleled the I^{131} uptake, there was considerable deviation; in some instances, thyroids with I^{131} uptakes as much as fourfold different were very similar in their total iodine (I^{127}) accumulations (Fig. 1).

The pattern of total iodine accumulation over periods of six to twenty-four hours was variable. In the majority of fasting subjects the hour-to-hour rates of uptake were relatively constant or decreased slightly over several hours. Following meals, rises occurred frequently, lasting two to three hours, sometimes to three times the fasting rates. These rises presumably were the result of ingestion of iodide with the food, and were particularly striking in hospitalized patients who were served iodized salt.

Small amounts of iodide were given (single doses orally of 10 micrograms of potassium iodide— 7.63 micrograms I^- —/kilogram body weight) to 15 additional euthyroid subjects; in 14, this was added to the I^{131} as carrier, and in the other patient was administered during the course of the uptake. In the instances in which they were determined, the serum iodide values were increased 1 to 3 micrograms per cent by this addition. In all except one person, the amounts of total iodide collected by the thyroid were higher than in those not given iodide, or were increased as a result of the

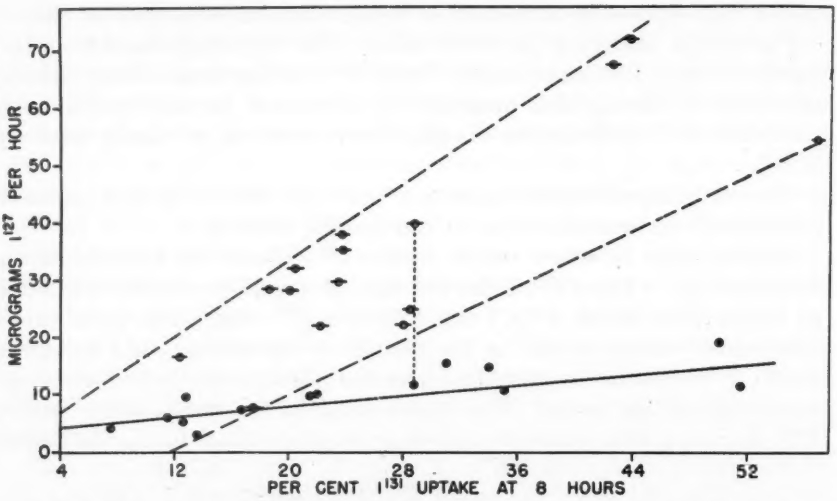


FIG. 1. The rate of total iodine utilization by the thyroid gland plotted against the radioiodine uptake in euthyroid subjects. The per cent of I^{131} collected in the thyroid at eight hours after administration of the dose is selected as an index of radioiodine uptake (abscissa). On the ordinate is represented the rate of I^{127} collection per hour. The solid circles signify that the subjects received no additional iodide; the serum iodide levels were usually less than 1 microgram per cent. The crossed open circles indicate that the subjects received 10 micrograms potassium iodide (7.63 micrograms I^-)/kilogram body weight, either as carrier with the I^{131} or, in one patient, during the course of the uptake (vertical dotted line connecting the solid circle and the crossed open circle).

addition. As a rule, this increase was greater for those individuals with the higher rates of I^{131} accumulation, although some overlapping was evident (Fig. 1).

In those 8 individuals who received additional small doses of iodide there were further increases in the amounts of iodide collected by the thyroid. The iodine accumulation by the thyroid varied directly with the serum levels of iodide, providing the latter were relatively low (Figs. 2 and 3).

As serum iodide levels above 6 to 12 micrograms per cent were attained with larger amounts of iodide, the organic binding of iodine in the thyroid was halted (Fig. 4). The values for serum iodide with which inhibition of binding was detectable were inversely related to the rate of I^{131} collection. Thus, in subjects with very slow rates of collection, serum iodide values in the upper part of the range were necessary before inhibition occurred,

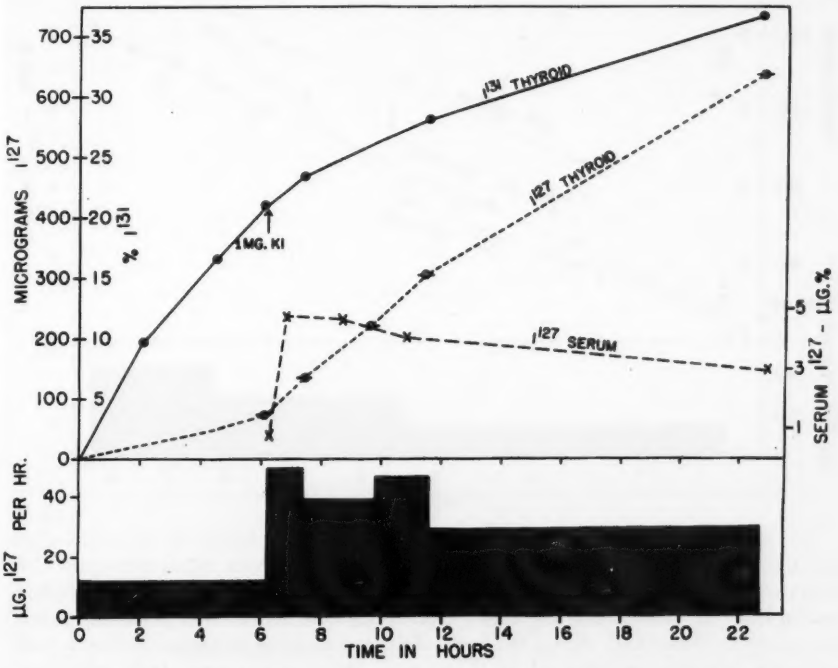


FIG. 2. The iodine utilization by the normal thyroid before and after administration of a small dose of iodide. The I^{131} accumulation curve is plotted against time to show the usual parabolic shape (solid line). The course of the I^{131} uptake was not changed by the dose of 1 milligram of potassium iodide which raised the serum level of iodide by 4 micrograms per cent (five times). However, the total (I^{127}) collection was increased approximately four times, from 11.7 micrograms/hour to 44.9 micrograms/hour, as shown by the dotted line and the bars.

whereas inhibition was attainable with levels around 6 micrograms per cent in others whose glands were very active.

Because of the appreciable amounts of iodine which could be accumulated and held as the iodide ion in the gland (see below), it was difficult to ascertain whether the cessation of organic binding due to iodide was grad-

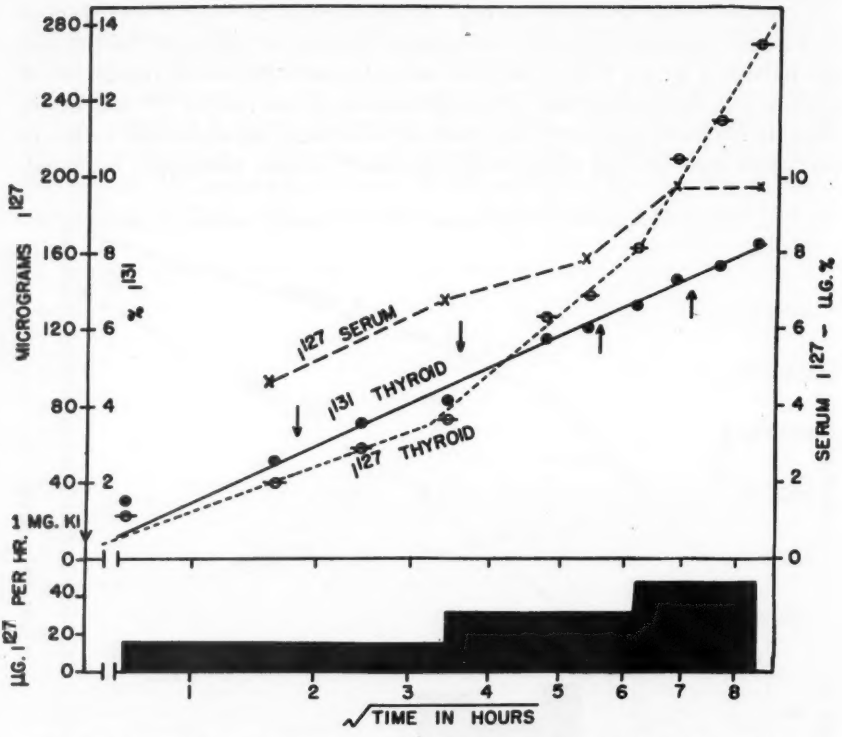


FIG. 3. The influence of several small doses of potassium iodide on the radioiodine and total iodine collection in a normal subject with a relatively inactive thyroid (I^{131} uptake 8 per cent in eight hours). The I^{131} accumulation is plotted against the "square root of time" to demonstrate the linear relationship. One milligram of potassium iodide was given as carrier and, during the test, additional doses of potassium iodide in half-milligram amounts, as indicated by the arrows. Although the serum level was raised to nearly 10 micrograms per cent by the total of 3 milligrams potassium iodide and the total iodine uptake was increased to 48 micrograms/hour, there was no inhibition of binding of iodine in this inactive gland.

ual as it appeared in a few instances, or always abrupt as it seemed in most subjects.

In the 13 thyrotoxic patients studied, there were large variations in the radioiodine collections and usually corresponding differences in total iodine accumulations. The average was 120 micrograms I^{127}/hour, and the range was from 44 to 265 micrograms/hour.

There was in these thyrotoxic glands a very large capacity for accumulating the iodide ion (5); even when organic binding of iodine was virtually completely inhibited by antithyroid drugs of the thiouracil type, such thy-

roids could collect as much as 40 per cent of a dose of I^{131} *as the iodide ion.* It was repeatedly demonstrated that such large quantities as 15 *milligrams* of iodide (I^{127}) could thus be held in glands in which binding had been halted. In such instances the prompt detection of inhibition by iodide was difficult, particularly when the dose was given during the course of accumulation, because of the large size of this "iodide space," which must be

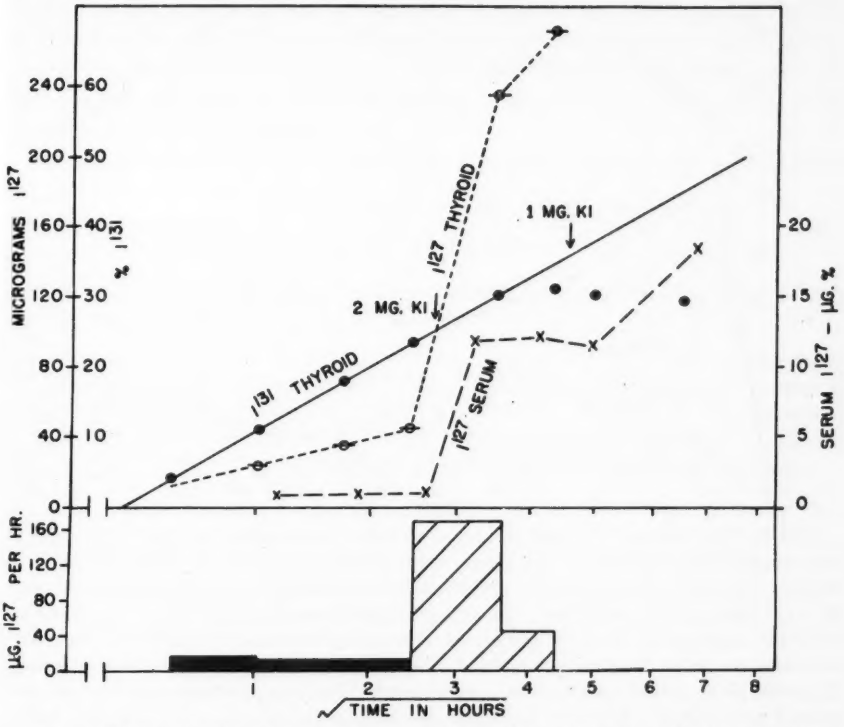


FIG. 4. The influence of a small but inhibitory quantity of iodide (2 milligrams potassium iodide) in a normal subject with a very active thyroid (I^{131} accumulation estimated by extrapolation to be 51 per cent at eight hours). The inhibition is shown by the cessation of accumulation of radioiodine soon after administration of the iodide. The large bars are hatched because the accumulations do not represent organically bound iodine solely. The larger hatched bar is spuriously high and represents a combination of : a) error in calculation (from continued uptake of high activity iodide before and during absorption of the added iodide); b) organic binding while the inhibitory levels were being achieved; and c) iodide ion collected after cessation of binding. The smaller hatched bar indicates an increment of iodide ion almost exclusively. That a part of the accumulated iodine was in the form of the freely diffusible iodide ion (unbound) is shown by the fall in I^{131} in the thyroid which occurred soon after the peak level was attained.

"filled" before blocking was evident. Since the uptake pattern in hyperplastic thyroids could not be fitted to a straight line as in normals, deviations from this line could not be utilized as an index of inhibition.

However, the characteristic pattern of collection exhibited by the inhibited hyperplastic gland was recognizable (5) (Figs. 5 and 6). This con-

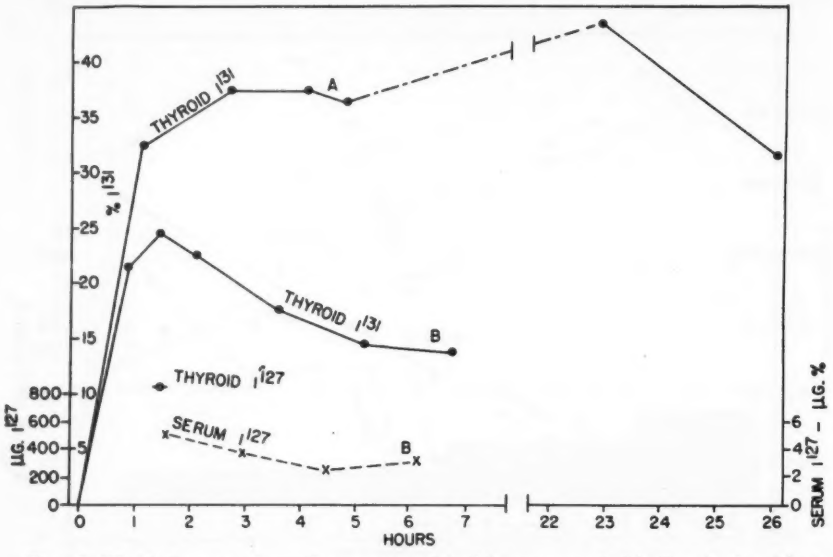


FIG. 5. The influence of small amounts of iodide on organic binding in 2 subjects with untreated thyrotoxicosis. Both received the iodide as carrier. In both, the characteristic shape of the curves denotes that the collection consisted largely of the iodide ion. In A (10 micrograms potassium iodide/kilogram body weight), there was some increase in I^{131} accumulation at the 23-hour interval, indicating that organic binding had occurred to some extent after this prolonged period. The decrease after thiocyanate administration (2 grams, given at the twenty-third hour) showed that an appreciable portion still remained as iodide ion, however. In B, (20 micrograms potassium iodide/kilogram body weight), with levels of serum iodide probably higher, the more rapid spontaneous decrease in the thyroid iodide I^{131} parallels the fall in serum iodide. The quantity of iodine in the thyroid in B, as shown by the crossed circle, was 827 micrograms during the second hour, mostly in the form of the iodide ion. No thiocyanate was given to this patient.

sisted of the rapid accumulation of 10 to 40 per cent of the I^{131}, which was usually at a maximum in two to three hours; following this there was a gradual or rapid fall as the radioactivity remaining in the gland in the form of freely diffusible iodide was diluted with serum iodide of progressively decreasing specific activity. The thiocyanate ion would cause discharge from the thyroid of all, or a large part of, that portion of iodine

which was present as the iodide ion (5, 6); this reaction was employed to identify the relative proportions of these two fractions and, hence, the degree of inhibition at any time (Figs. 5 and 6).

By such means, therefore, it was demonstrated in 8 additional thyrotoxic patients that with very low levels of serum iodine—less than 5 micrograms per cent—organic binding could be prevented in hyperplastic glands. The inverse relationship observed in normal subjects between the level of iodide in the serum at which inhibition occurred and the thyroid iodide-concentrating ability (or rate of uptake) could be extended to include thyrotoxic patients with hyperplastic thyroids. Inhibition could be produced with much lower levels of serum iodide in thyrotoxic patients than were necessary in normal subjects.

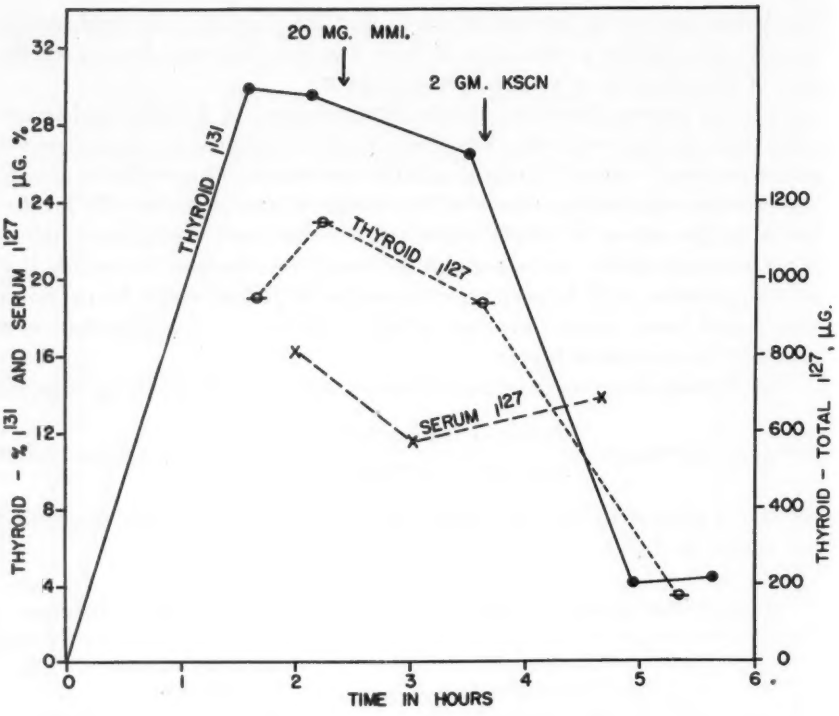
The thyroid *clearance* of serum iodide is readily calculated for each period from the expression: $\frac{\text{Thyroid } I^{131} \text{ accumulation per hour}}{\text{Average } I^{131} \text{ serum concentration}}$. Average values for the 3 normal individuals whose iodine accumulations are illustrated, are shown in Table 1.

TABLE 1. THE AVERAGE THYROID IODIDE CLEARANCES IN 3 NORMAL PERSONS

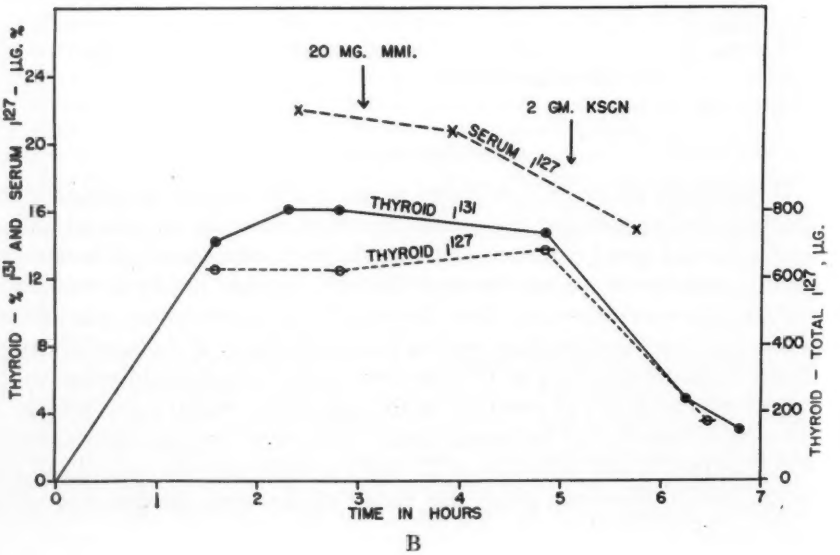
	Thyroid I^{131} accumulation (per cent at 8 hours)	Thyroid clearance of iodide	
		ml./hour	ml./minute
Fig. 2	24	1115	18.6
Fig. 3	8	430	7.2
Fig. 4	51.5 (by extrapolation)	1720	28.7

DISCUSSION

Without the studies of concurrent serum iodide levels and, especially, of the total iodine entering the gland, the effect of iodide on iodine binding in the thyroid could not be assessed by the radioiodine method because of the uncontrolled factor of chemical dilution. It could not be certainly ascertained in some situations that the total hormone formation was altered —*i.e.*, that apparent blocking was not the result simply of chemical dilution. Thus, a minute quantity of I^{131}, the detection of which could conceivably be beyond the limits of accuracy of the apparatus, would carry with it, if the specific activity of the serum iodide were very low, the same amount of I^{127} as measurable amounts of I^{131} with a higher specific activity of the serum iodide. However, since this factor of chemical dilution was quite


20 MG. MMI.
2 GM. KSCN
THYROID I^{131}
THYROID I^{127}
SERUM I^{127}
THYROID - % I^{131} AND SERUM I^{127} - µG. %
THYROID - TOTAL I^{127}, µG.
TIME IN HOURS

A


20 MG. MMI.
2 GM. KSCN
SERUM I^{127}
THYROID I^{131}
THYROID I^{127}
THYROID - % I^{131} AND SERUM I^{127} - µG. %
THYROID - TOTAL I^{127}, µG.
TIME IN HOURS

B

large in some thyroids (with slow rates of iodine turnover) before the I^{131} accumulation stopped (Fig. 3), whereas it was small in others (with relatively rapid uptakes), it could be inferred that cessation of I^{131} collection indicated actual inhibition of binding. Thus, the observations of Wolfe and Chaikoff in the rat were extended to man.

The observed values for serum iodide in patients who had not received iodine medication, 1 microgram per cent or less, agree well with those obtained by sensitive microchemical methods. Our results depend upon chemical analysis of iodine in the urine, which is a relatively easy chemical procedure. Since the iodine content is usually above 10 micrograms per cent, 10 to 20 cc. of urine can be readily analyzed. Hence it is felt that the results by this indirect method on serum are at least as accurate as those obtained by direct analyses.

From the observations reported here it may be deduced that in each individual the thyroid extracts a certain fraction of the iodide from the blood. This fraction remains constant, at least for a short time, with increasing levels of serum iodide until inhibition is attained. Presumably in euthyroid subjects the quantity of pituitary thyrotropin available is a most important factor in determining the size of the fraction of serum iodide extracted by the thyroid. The rate of I^{131} accumulation is an indication of the magnitude of the fraction, and, hence, of the potential capacity for hormone formation within the limits discussed in the next paragraph. However, in order to know how much iodine is being used for synthesis at any time, it is necessary to determine the specific activity of the metabolized iodine. Therefore the assumption that a rapid accumulation of radioiodine by the thyroid indicates a large total iodine utilization, such as accompanies thyrotoxicosis, may in certain instances be fallacious (Fig. 1). These same limitations are applicable when these functions are expressed as thyroid clearance of serum iodide.

Our data are consistent with the theory (1) that the concentration of iodide ion in the thyroid cells, rather than the serum iodide level, is the ultimate consideration governing the amount of iodide necessary to produce inhibition in a given instance. The thyroid cell iodide concentration is a function, not only of the serum iodide level, but also of the ability of the thryoid to

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FIG. 6. The influence of larger amounts of iodide on organic binding of iodine in the thyroid glands of 2 additional patients with thyrotoxicosis. In both subjects 5 milligrams of potassium iodide were given by mouth (A, 40 minutes; B, 90 minutes) before the I^{131}. In both, the serum levels of iodide were in excess of the concentration required to produce inhibition of binding. The left vertical arrows ("MMI") indicate the administration of large doses of the potent antithyroid drug, 1-methyl,2-mercaptoimidazole; the reasons for this are discussed in the text. In each patient there was a small residual fraction of radioactivity in the gland following the action of thiocyanate. The interpretation of this finding is also undertaken in the text.

concentrate the iodide ion from the serum. This latter is probably largely controlled by pituitary thyrotropin in normal individuals. Further evidence for the above theory was obtained by Raben (7) after he noted that his laboratory rats, with comparatively atrophic glands from a relatively high iodine diet, required much larger amounts of iodide to produce inhibition than the rats described by Wolff and Chaikoff. The only discernible difference in the animals from the two laboratories was that Wolff and Chaikoff's animals had relatively hyperplastic glands, with a high thyroid /serum iodide ratio. Direct confirmation was provided when Raben administered small amounts of thiocyanate to animals with serum iodides above the inhibitory levels. In these amounts this drug had the effect of discharging part of the iodide from the thyroid cells (6) without appreciably altering the serum iodide levels. Following this decrease in the concentration of iodide in the thyroid cell, organic binding was resumed—and in the presence of the formerly inhibitory levels of serum iodide.

Although the effect of small amounts of iodine in increasing hormone formation is implied in the use of the drug in the prophylactic treatment of simple goiter, the augmentation of iodine utilization has not hitherto been directly demonstrated in man. In animals, on the other hand, this effect has been repeatedly shown (1, 8). It is interesting that Wolff and Chaikoff's data reveal that the level of organic I^{127} binding was very high with a dose of iodide (10 micrograms) below the inhibition level. The studies reported herewith imply that large doses of iodide are undesirable in situations in which it is the purpose to increase hormone production, as in the prevention of iodine-deficiency goiter.

Our results indicate that only very small quantities of iodide are necessary to inhibit organic binding in the thyrotoxic thyroid gland. This correlates well with the observations of Thompson *et al.* (9) that a maximal response in thyrotoxicosis may be regularly obtained by single daily doses of 6 milligrams of iodine. The effective dose could conceivably be smaller if it were divided.

In thyrotoxic subjects (5), even after large doses of potent antithyroid compounds such as 100 milligrams of 2-mercaptoimidazole, a fraction of accumulated radioiodine often remained in the thyroid gland following ingestion of thiocyanate. This portion of radioactivity which was not discharged from the gland amounted to as much as 20 per cent in some instances. There was evidence that organic binding was virtually completely inhibited by these amounts of drug. Hence, it was felt that most of this residual radioactivity was in the form of the iodide ion, but that the thiocyanate had failed to reduce the thyroid/serum iodide ratio to unity in these extremely hyperplastic glands.

In the present study, more than the expected amounts of radioiodine remained in the thyrotoxic thyroid glands after thiocyanate administration

This occurred with serum iodide levels considered to be inhibitory. In view of Raben's experiments this was thought to be the result of resumption of organic binding as, during the process of discharge, the iodide was decreased to sub-inhibitory levels in the thyroid cells. In order to obviate this difficulty, an inhibiting dose of antithyroid compound was given before the thiocyanate so as to prevent organic binding of iodine *during the period of discharge of iodide* (Fig. 6). Obviously this had no effect on the inhibition of binding by iodide *previous* to administration of the antithyroid drug. With this added precaution, it could be demonstrated that the indicated concentrations of iodide ion produced about the same degree of suppression of the thyroid glands of thyrotoxic subjects as did large doses of antithyroid drugs such as mercaptoimidazole (Fig. 6). However, it could not be stated with certainty that inhibition was complete; it was impossible to exclude the organic binding of a small amount of iodine.

These acute experiments do not provide a clue as to what happens later during the course of the treatment of Graves' disease to prevent a full metabolic response or to explain the relapses which occur while full doses of iodine are being given. The suggestion has been made recently that failure to maintain inhibitory levels of plasma iodide may account for the exacerbation of the hyperthyroid state (10). If this occurred, even for a short period, large amounts of iodine would probably be organically bound, because at iodide levels slightly below those producing inhibition, conditions would be optimal for maximal hormone production. On the other hand, the quantities of iodine customarily prescribed (of the order of 100 milligrams daily) should be adequate to maintain inhibitory blood iodide levels. Therefore, fundamental alterations in the iodine metabolism of the thyrotoxic thyroid gland (or in the urinary excretion of iodine) may take place during treatment of Graves' disease with iodine, which will explain this phenomenon in other ways.

SUMMARY AND CONCLUSIONS

A method is described for the direct measurement of total iodine accumulation by the thyroid, using the thyroid I^{131} uptake and the specific activity of the simultaneously excreted urine. If, at the same time, the radioactivity in the serum is determined, the serum iodide can be calculated:

$$\text{serum } I^{127} = \frac{\text{serum } I^{131} \times \text{urine } I^{127}}{\text{urine } I^{131}}.$$

By this method the iodine collection by the thyroids in 14 euthyroid individuals who had not received added iodide average 10 micrograms /hour. In 13 thyrotoxic persons, the corresponding figure was 120 micrograms/hour. With small amounts of added iodide, the total iodine uptake was increased. With larger quantities, inhibition of organic binding of

iodine in the thyroid gland occurred. In general, inhibition seemed to be determined by the level of iodide in the thyroid cell, which was a function both of the ability of the cell to concentrate iodide from the serum and the amount of iodide available in the serum. The serum iodide levels with which inhibition could be produced in thyrotoxic subjects were 5 micrograms per cent or less, whereas a higher value, between 6 and 12 micrograms per cent, was necessary to stop organic binding in the less hyperplastic glands of euthyroid individuals. These data are the results of acute experiments. No clue is provided to explain the relapses which occur during the course of treatment of Graves' disease with full doses of iodine. Alterations in the above reactions may occur after a period of iodinization.

Acknowledgments

The author is grateful to Dr. E. B. Astwood for helpful suggestions during the course of the study and in the preparation of the manuscript, and to Mrs. Adele Bissell Grady, who performed the chemical analyses for urinary iodine and prepared the illustrations.

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THE ANTITHYROXINE ACTIVITY OF THYROXINE ANALOGS*†

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SINCE the discovery of the inhibitory action of para-aminobenzoic acid on the sulfonamides, the concept of antagonistic action between compounds closely related structurally has been applied to many fields of biologic activity, as reviewed recently by Woolley (1947 (1)). In 1946 (2) Woolley reported on the synthesis of a series of compounds which were antagonistic to thyroxine. Using as a criterion of such activity the ability of the compounds to protect tadpoles against lethal doses of thyroxine, he found that several ethers of N-acetyl-diiodotyrosine possessed the property of inhibiting the activity of thyroxine. Some of these compounds exhibited in addition a weak thyroxine-like effect.

To explore further the possibility of antagonizing the action of thyroxine by compounds related to it structurally, a series of substituted thyronine compounds were examined for their antithyroxine activity. These compounds were more closely related structurally to thyroxine than the compounds studied by Woolley. They were synthesized by Niemann (1941, 1941 b, 1944). Seven compounds were available for study,[1] namely:

1. Thyronine
2. 3′-Fluorothyronine
3. 3′-Fluoro-3,5-diiodothyronine
4. 3′,5′-Difluoro-3,5-diiodothyronine
5. 3′-Fluoro-5′-iodo-3,5-diiodothyronine
6. 2′,6′-Diiodothyronine
7. 3′,5′-Diiodo-4 (4′-hydroxyphenoxy) 3,5-diiodo hippuric acid.

The structural configurations of these compounds are depicted in Figure 1.

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[1] Dr. Carl Niemann of the California Institute of Technology kindly supplied all the thyroxine analogs used in these experiments.

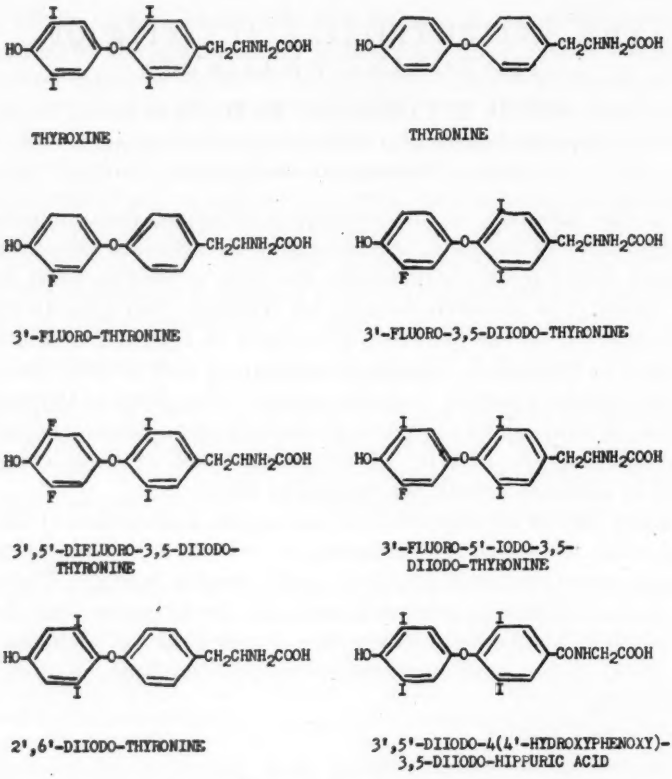

FIG. 1. Structural configuration of thyroxine and thyroxine analogs.

Because of the close structural similarity between these compounds and thyroxine, all of these thyroxine analogs were studied for their thyroxine-like activity as well as their possible antithyroxine activity. Four of the compounds were fluorine-substituted thyronine compounds, and it was thought to be of considerable interest to determine what effect the substitution of fluorine for iodine would have on the activity of thyroxine.

METHODS

Astwood, *et al.* (1943 (6)) and MacKenzie and MacKenzie (1943 (7)) demonstrated the ability of a group of thiourea compounds and the sulfonamides to inhibit the formation of thyroid hormone, with a resulting enlargement of the thyroid gland because of the increased output of anterior pituitary thyrotropic hormone. Dempsey and Astwood (1943 (8)) showed that the administration of graded doses of thyroxine to thiouracil-

treated rats resulted in a quantitative inhibition of the hyperplasia of the thyroid gland caused by thiouracil, and these authors demonstrated the use of this phenomenon as a method for the assay of thyroid activity. Reineke, Mixner and Turner (1945 (9)) showed the close correlation between this method of studying thyroid activity and the standard metabolic method.

In the experiments reported here the thyroxine-like activity of each compound was determined by injecting the material into thiouracil-treated rats and comparing the thyroid gland weights with those of rats treated with thiouracil alone. Decrease in weight indicated thyroxine-like activity. A comparison of the decrease in thyroid weight with that attained by a standard dose of thyroxine (in this case 5.0 micrograms) indicated the relative potency of the two compounds. The ability of these compounds to antagonize thyroxine was determined by injecting each compound into thiouracil-treated rats which were receiving 5.0 micrograms of thyroxine. If the compound had the property of interfering with the action of thyroxine, the decrease in size caused by thyroxine would be inhibited and the hyperplasia usually brought about by thiouracil treatment would still be present.

The experiments were performed on male rats of the Sprague-Dawley strain weighing approximately 120 grams at the start of the experiment. They were kept in small cages with 2 rats in each cage. Food was Purina laboratory chow given *ad libitum*. The thiouracil was given as a 0.1 per cent solution in the drinking water. Each compound was tested on a group of 10 animals, unless otherwise indicated. In each series of experiments, the animals were treated for ten days with thiouracil, during which time they received daily injections of the compounds being tested. On the eleventh day the rats were killed with ether, the thyroid glands carefully dissected out and weighed on the torsion balance and the weight of the thyroid gland per 100 grams of body weight were calculated. For each group the mean and standard deviation were determined and, where indicated, significant differences between two means were determined by analysis of variance.

RESULTS

As a preliminary study, each of the 7 thyroxine analogs was tested in equimolecular doses for its thyroxine-like and antithyroxine activity, using 5.0 micrograms of thyroxine as a standard. This dose of thyroxine was found to be the minimum dose necessary to prevent completely the hyperplasia of the thyroid gland in rats treated for ten days with thiouracil. The experiments were performed in successive ten-day periods. Each new compound was tested by using 4 groups of rats. All the rats received thiouracil

as a 0.1 per cent solution in the drinking water. In addition, the different groups received as follows:

Group 1. Nothing.
Group 2. Five micrograms of thyroxine.
Group 3. Thyroxine analog.
Group 4. Five micrograms of thyroxine plus thyroxine analog.

Groups 1 and 2 were used as controls for more than one compound when the tests were being run simultaneously. The dosage of the thyroxine analog was chosen so that each compound was approximately equivalent to 150 times the thyroxine dose on a molecular weight basis.

TABLE 1. THE THYROXINE-LIKE AND ANTITHYROXINE ACTIVITY OF SOME THYROXINE ANALOGS

Group	1	2	3	4
Thyroxine analog plus dose	Thiouracil alone	Thiouracil + thyroxine (5 micrograms per rat per day)	Thiouracil + thyroxine analog	Thiouracil + thyroxine (5 micrograms) + thyroxine analog
Thyronine (260 micrograms per rat per day)	15.96 ±2.45*	7.83 ±1.12	14.87 ±2.32	7.21 ±1.36
3′-fluorothyronine (277 micrograms per rat per day)	20.19 ±5.04*	9.79 ±2.63	20.14 ±4.23	7.72 ±0.88
3′-fluoro-3,5-diiodothyronine (515 micrograms per rat per day)	20.19 ±5.04	9.79 ±2.63	5.36 ±0.57	5.24 ±0.61
3′,5′-difluoro-3,5-diiodothyronine (545 micrograms per rat per day)	19.79 ±3.65	8.33 ±2.22	6.89 ±1.79	5.44 ±0.95
3′-fluoro,5′-iodo-3,5-diiodothyronine (635 micrograms per rat per day)	18.79 ±3.65	8.33 ±2.22	5.60 ±0.99	6.13 ±0.70
2′,6′-diiodothyronine (500 micrograms per rat per day)	15.47 ±2.30	8.50 ±2.25	17.19 ±2.28	13.09 ±1.42
	18.13 ±1.63	10.30 ±1.30	17.69 ±3.22	16.11 ±2.57
3′,5′-diiodo-4(4′-hydroxyphenoxy) 3,5 diiodo hippuric acid (755 micrograms per rat per day)**	15.47 ±2.97	7.61 ±2.11	11.34 ±3.01	6.47 ±0.97

* Mean thyroid weight in milligrams per 100 Gm. body weight plus standard deviation.

** Only 9 rats used in each of these groups.

The results of these experiments are summarized in Table 1. In examining the table, if one compares the results in groups 1 and 3 for any given compound, one can determine the presence of thyroxine-like activity. A significant decrease in thyroid weight in group 3 as compared with group 1 indicates that the compound has thyroxine-like activity because the thiouracil hyperplasia is suppressed. A comparison of group 3 with group 2 gives some indication of range of potency. A comparison of group 2 with group 4 gives information concerning the antithyroxine activity of any given compound. A significant increase in thyroid weight in group 4 over that in group 2 shows that the thyroxine activity is being inhibited.

Therefore it can be seen that the compound 2′,6′-diidothyronine definitely inhibited the activity of thyroxine. In two separate experiments this compound almost completely inhibited the suppressing effect of 5.0 micrograms of thyroxine on thiouracil hyperplasia. None of the other compounds exhibited any antithyroxine activity. In fact, several of them exhibited thyroxine-like activity, some to a marked degree.

To elucidate further the thyroxine-inhibiting activity of 2′, 6′-diidothyronine the compound was given to a group of normal rats, receiving no other treatment for a period of ten days, in a dose of 500 micrograms per day. At the end of this period the thyroid glands were weighed and also examined histologically. There was found to be no effect of this compound on thyroid weight (Table 2) or histologic appearance compared with control rats. Since it is generally believed that injected thyroxine probably becomes combined in some way within the body before it is active, it was postulated that perhaps 2′,6′-diiodothyronine antagonizes the action of injected thyroxine by competing with it *in vivo* for some type of combination, whereas when the 2′,6′-diiodothyronine is given to rats whose thyroid activity comes solely from the normally functioning thyroid gland, the combination has already occurred, and any competing analog would be ineffective.

TABLE 2

Treatment	No. of rats	Thyroid weight per 100 Gm. body weight (milligrams) Mean ±S.D.
Control	5	7.90 ±0.76
2′,6′-Diiodothyronine (500 micrograms per rat per day)	6	7.41 ±0.88

In order to put this hypothesis to the test, the ability of 2′,6′-diiodothyronine to antagonize the action of thyroglobulin was determined. In thyro-

globulin the thyroxine is already in combination as one of the constituent amino-acids. The thyroglobulin preparation used in these experiments was a relatively pure preparation[2] which could be repeatedly injected subcutaneously without eliciting any untoward reactions. It contained 28.9 mg. per 100 cc. of total organic iodine, of which 5.75 mg. per 100 cc. was thyroxine iodine. After a preliminary experiment in which it was found that 0.012 cc. of the thyroglobulin preparation was approximately equivalent to 5.0 micrograms of thyroxine, an experiment was set up in which larger

TABLE 3. THE ANTAGONISTIC ACTION OF VARYING DOSES OF 2′,6′-DIIODOTHYRONINE AGAINST VARYING DOSES OF THYROGLOBULIN AND THYROXINE

The rats received thiouracil as a 0.1 per cent solution in the drinking water

Group	Thyroglobulin, cc.	Thyroxine, micrograms	2′,6′Diiodothyronine, milligrams	Thyroid weight per 100 Gm. body weight (milligrams) Mean ±S.D.
1	0	0	0	15.96 ±2.45
2	0	5	0	7.83 ±1.12
3	0	7	0	6.11 ±0.83
4	0	7	2.5	11.71 ±0.97
5	0.012	0	0	6.22 ±0.90
6	0.012	0	2.5	10.30 ±1.77
7	0.023	0	0	4.96 ±0.64
8	0.023	0	5.0	5.70 ±0.84
9	0	0	0	5.62 ±0.74*

* No thiouracil.

doses of 2′,6′-diiodothyronine than had been used previously against thyroxine were tested against varying doses of thyroglobulin and in addition against 7.0 micrograms of thyroxine. The results are shown in Table 3, where it can be seen that whereas 2.5 milligrams of 2′,6′-diiodothyronine was able partially to inhibit the activity of 0.012 cc. of thyroglobulin, 5.0 milligrams of 2′, 6′-diiodothyronine had no inhibiting effect whatsoever on 0.023 cc. of thyroglobulin. Furthermore, 2.5 milligrams of 2′,6′-diiodothyronine only partially inhibited the activity of 7 micrograms of thyroxine, whereas in previous experiments it was shown that 500 micrograms of 2′,6′-diiodothyronine could almost completely antagonize the action of 5.0 micrograms of thyroxine. These experiments demonstrated that 2′,6′-diido-

[2] The thyroglobulin was kindly supplied by Dr. Robert Kroc of the Maltine Company.

TABLE 4. A COMPARISON OF THE POTENCY OF 3′-FLUORO-3,5-DIIODOTHYRONINE WITH THYROXINE

Group	Treatment: All rats received 0.1% thiouracil to drink. In addition:	Thyroid weight per 100 Gm. body weight (milligrams) Mean ±S. D.
1	0	16.03 ±1.80
2	Thyroxine—5 micrograms per day	7.66 ±1.55
3	3′-Fluoro-3,5-diiodothyronine 64.8 micrograms per day≏20 ×thyroxine	10.88 ±2.18
4	3′-Fluoro-3,5-diiodothyronine 140 microgram per day≏40 ×thyroxine	6.53 ±0.95

TABLE 5. A COMPARISON OF THE POTENCY OF 3′,5′-DIFLUORO-3,5-DIIODOTHYRONINE WITH THYROXINE*

Group	1	2	3
Dose of 3′,5′-difluoro-3,5-diiodothyronine	Thiouracil alone	Thiouracil + 5 micrograms of thyroxine	Thiouracil + 3′,5′-difluoro-3,5-diiodo-thyronine
220 micrograms per day≏60 ×thyroxine	18.96 ±3.40	5.55 ±0.85	6.11 ±1.13
108 micrograms per day≏30 ×thyroxine	16.03 ±1.79	7.66 ±1.55	10.73 ±2.56
72 micrograms per day≏20 ×thyroxine	16.03 ±1.79	7.66 ±1.55	13.82 ±2.11

* Each value represents the mean thyroid weight in milligrams per 100 Gm. body weight plus standard deviation for each group.

TABLE 6. A COMPARISON OF THE POTENCY OF 3′-FLUORO-5′-IODO-3,5-DIIODOTHYRONINE WITH THYROXINE*

Group	1	2	3
Dose of 3′-fluoro-5′-iodo-3,5-diiodothyronine	Thiouracil alone	Thiouracil + 5 micrograms + thyroxine	Thiouracil + 3′-fluoro-5′-iodo-3,5-diiodo thyronine
86.2 micrograms per day≏20 ×thyroxine	18.96 ±3.40	5.55 ±0.85	6.56 ±1.04
43.1 micrograms per day≏10 ×thyroxine	18.96 ±3.40	5.55 ±0.85	5.96 ±0.73
21.5 micrograms per day≏5 ×thyroxine	16.03 ±1.79	7.66 ±1.55	5.39 ±0.36
12.9 micrograms per day≏3 ×thyroxine	16.03 ±1.79	7.66 ±1.55	5.54 ±1.03

* Each value represents the mean thyroid weight in milligrams per 100 Gm. body weight plus standard deviation for each group.

thyronine can antagonize the action of injected thyroglobulin as well as that of thyroxine, but the quantitative relations are certainly not clear cut.

To return to the other thyroxine analogs, examination of Table 1 demonstrates that neither thyronine nor 3′-fluorothyronine showed any thyroxine-like activity in a dose 150 times that of thyroxine. The other fluorine-substituted compounds all showed thyroxine-like activity, and in the dose given, *i.e.* 150 times the dose of thyroxine, were more effective than 5 micrograms of thyroxine. Therefore, further experiments were performed, using smaller doses of these compounds, to determine their relative potency. The data on these compounds are presented in Tables 4, 5 and 6. These tables show that the activity of 3′-fluoro-3, 5-diiodothyronine lies between one-twentieth and one-fortieth that of thyroxine, and that of 3′,5′-difluoro-3,5-diiodothyronine is between one-thirtieth and one-sixtieth that of thyroxine. In the case of 3′-fluoro-5′-iodo-3, 5-diiodothyronine, it was found that this compound is at least one-third as active as thyroxine, and probably more so.

The final compound which was tested, namely 3′,5′-diiodo-4 (4′-hydroxyphenoxy) 3-5-diiodohippuric acid was found to have a weak but definite thyroxine-like activity. A dose 150 times that of thyroxine showed an activity less than that of 5 micrograms of thyroxine, showing that this compound has less than 1/150 the activity of thyroxine.

DISCUSSION

The results of these experiments demonstrate that among the group of thyroxine analogs studied, one of them, namely 2′,6′-diiodothyronine, had the ability to antagonize the action of thyroxine when the latter was injected into rats treated with thiouracil. Furthermore, it was also shown that this compound could inhibit the activity of injected thyroglobulin. It is interesting to note that 2′,6′-diiodothyronine was the only compound in which the substitutions were in the 2′,6′ position on the phenyl ring. In all the other compounds, the iodine or fluorine substitutions were in 3,5 or 3′,5′ position on the phenyl ring. These compounds had either thyroxine-like activity or no activity at all; none of them showed any antithyroxine activity.

The mechanism of the inhibitory action of 2′,6′ diiodothyronine on thyroxine is not clear from these experiments. In the doses used, the antagonist had no demonstrable effect on the thyroid gland of normal untreated rats, suggesting that its action is not related to the production of thyroid hormone by the gland, such as is seen with thiouracil and related compounds. It is generally believed that thyroglobulin is broken down to simple polypeptides containing thyroxine before it circulates in the blood stream, and presumably before it acts on tissue cells. If it can be assumed that

2′,6′-diiodothyronine exerts its effectiveness by competing with thyroxine in some essential reaction, the data suggest that the injected thyroglobulin is broken down to a point where the thyroxine constituent has a certain lability before it is active.

The quantitative relationships in the antagonism between 2′,6′-diiodothyronine and thyroxine and thyroglobulin are unusual. Although 0.012 cc. of thyroglobulin is partially inhibited by 2.5 mg. of 2′,6′-diiodothyronine, double this dose of thyroglobulin is not affected at all by a twofold increase in the dose of 2′,6′-diiodothyronine. Although 0.5 mg. of 2′,6′-diiodothyronine almost completely antagonizes the action of 5 micrograms of thyroxine, 7 micrograms of thyroxine are only partially antagonized by 5 times the dose of 2′,6′-diiodothyronine. It would seem that the ability of 2′,6′-diiodothyronine to antagonize these thyroid preparations is more related to the dose of the latter than the dose of antagonist used. As the dose of the thyroid preparation approaches a maximal dose, 2′,6′-diiodothyronine is less effective, even in larger doses.

As far as the activity of the other thyroxine analogs are concerned, there are some interesting points relative to the relationship between structure and function of the thyroxine molecule. The inactivity of thyronine is of course well known (Gaddum, 1927 (10), 1929 (11)). The complete inactivity of 3′ fluorothyronine is further evidence for the necessity of having a 3,5 substitution with iodine on the first ring. All of the compounds studied here which had such a 3,5 substitution with iodine were found to exhibit thyroxine-like activity, although in varying degrees of potency, depending on other changes in the molecule.

Both Abderhalden (1928 (12)) and Gaddum (1929 (11)) studied the activity of a series of chlorine and bromine substituted thyronines, in each of which there were substitutions in all four of the 3,5,3′,5′ positions. The tetrabrome compound had weak thyroxine-like activity, as did compounds which had combinations of both iodine and bromine and iodine and chlorine. However, neither author has given sufficient quantitative data to assess the comparative effectiveness of these compounds. In the experiments reported here it was possible to compare the effectiveness of a single fluorine atom in the second ring at the 3′ position with that of two fluorine atoms in the second ring at the 3′,5′ positions, when iodine is present in the 3,5 position. The data obtained showed that the compound containing the two fluorine atoms is no more effective than the compound containing one fluorine atom, and in all probability, these fluorine substitutions do not enhance the activity of 3,5-diiodothyronine. This could be more directly proven by a comparison of the fluorine-substituted compounds with 3,5-diiodothyronine itself.

The picture becomes very different when one iodine atom is substituted

in the second ring along with one fluorine atom, as in the compound 3′-fluoro-5′-iodo-3,5,-diiodothyronine. The activity of this compound closely approaches that of thyroxine. This demonstrates that the presence of only one iodine atom in the second ring results in a compound which is almost as active as thyroxine, which has two iodine atoms in the second ring. It would be of interest to know whether the fluorine atom in the 3′ position is contributing anything to this activity. In view of the relative inactivity of the additional fluorine atoms in the compounds discussed above, this is doubtful.

A comparison of the activity of thyroxine and thyroglobulin as determined in these experiments, gives corroboration of the well-known fact that on the basis of thyroxine iodine, thyroglobulin is more active than

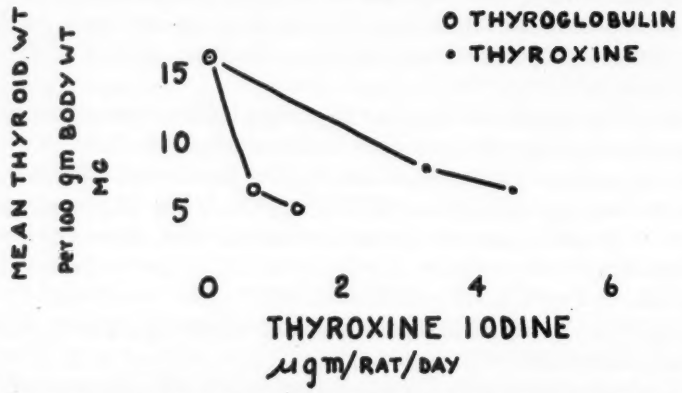

FIG. 2. The comparative effectiveness of thyroxine and thyroglobulin in inhibiting the thyroid gland weight in rats treated with thiouracil.

thyroxine. The thyroglobulin preparation had a value of 5.75 mg. of thyroxine iodine per 100 cc. Thyroxine has an iodine content of 65.4 per cent. The comparative effectiveness of these two compounds in suppressing thiouracil hyperplasia is plotted in Figure 2 on the basis of the thyroxine content of each compound. This graph shows conclusively that per unit of thyroxine iodine, thyroglobulin is much more effective than thyroxine. These results are significant, in that both compounds were injected subcutaneously, thus eliminating any differences on the basis of variations in absorption or destruction in the gastro-intestinal tract.

Harington in 1933 (14) showed that a peptide containing thyroxine obtained from thyroglobulin by enzymatic hydrolysis was more active than thyroxine alone and he postulated that "the activity of thyroxine can be enhanced by combination with other amino acids which occur in thyroglobulin." " . . . thyroxine is not to be regarded as itself the complete active

principle, but is rather to be considered as the constituent which confers specific physiological properties upon a more complex molecule."

SUMMARY

Seven thyroxine analogs were tested for antithyroxine and thyroxine-like activity on rats treated with thiouracil. One of the compounds, 2′, 6′-diiodothyronine was able to antagonize the action of thyroxine in a dose 150 times that of the thyroxine. It also showed an action antagonistic to injected thyroglobulin.

Two of the compounds, thyronine and 3′-fluorothyronine, had neither thyroxine-like or antithyroxine activity. The compounds 3′-fluoro-3,5-diiodothyronine and 3′,5′-difluoro-3, 5-diiodothyronine were found to have weak thyroxine-like activity, the former one-twentieth to one-fortieth, and the latter one-thirtieth to one-sixtieth, that of thyroxine. 3′-Fluoro-5′-iodo-3, 5-diiodothyronine was found to have an activity close to that of thyroxine.

3′,5′-Diiodo 4(4′-hydroxyphenoxy) 3,5-diiodohippuric acid was found to have very slight thyroxine-like activity.

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HENRY S. PLUMMER, M.D.*

Presidential Address
American Goiter Association

ARNOLD S. JACKSON, M.D.
From the Jackson Clinic, Madison, Wisconsin

AMONG the great physicians and surgeons who have contributed most to our knowledge of goiter in the past, we think of Kocher, Graves, Joll, Basedow, Crile, C. H. Mayo, Halsted and Plummer. There have been others whose scientific achievements might merit high recognition in the field of thyroid disease but whose work has not left such a deep imprint.

Of those who achieved world recognition for their work on goiter, none received greater acclaim than did a former president of this Association—Doctor Henry S. Plummer. Through his contribution on the use of Lugol's solution in the preoperative treatment of exophthalmic goiter, his name became known to physicians in every civilized country. Yet this idea which meant the saving of so many thousands of lives, and which so lessened the worries of physicians and surgeons, was only one of the remarkable advancements he brought to this field of medicine.

Of the great men in medicine and the other professions whom I have had an opportunity to know, there has been but one genius: Henry Plummer. He was a man who, no matter in what field—architecture, engineering, horticulture, conservation, tool craft, business administration, statistics, roentgenology, bacteriology, otolaryngology or bronchoscopy, to mention only a few of his many accomplishments—would have been outstanding.

Yet his great ability and numerous accomplishments were not widely known, because he wrote very little and was not given to speaking. It was my good fortune, as one of his Fellows, to work out a thesis on the study of the thyroid gland and its diseases under his guidance. At that time, no particular attention was attached to this work, as we all felt that Doctor Henry would some day publish a book on this subject. However, some ten years after I had left Rochester, I met Doctor Will Mayo at a medical meeting dinner in Green Bay. He said that, in his opinion, Doctor Plummer never would write a book on Goiter, and he urged me to start work on another edition of my book. Not long after my talk with Doctor Mayo, Doctor

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Plummer was taken ill and at much too young an age, passed away. It was indeed regrettable that such a genius was not spared for a few years more, for his contributions to our knowledge of goiter might have solved many of the problems that still confront us.

He had an engineering type of mind. An engineer is not satisfied with problems that are not completed and, of course, cannot be satisfied with inaccuracies. He was a creative thinker; his mind went from one constructive problem to another. When he had completed an investigation or had carried an investigation to a point where he thought that in our present knowledge its limits had been reached, his tendency was to lose interest in it. His primary interest was in creation—not in the publication of the results of his creative work.

As did many other great Americans, *e.g.*, Franklin, Jefferson and Edison, Henry Plummer grew up in rather humble surroundings: not in a log cabin, to be sure, for his father was a fairly successful country doctor, residing in Hamilton, Minnesota, where Henry was born in 1874. In this small-town atmosphere he attended grade school and later the Spring Valley High School. He entered the University of Minnesota and after two years there, went to Northwestern University Medical School from which he was graduated in 1898.

After graduation from medical school, he spent three years in practice in Racine, Minnesota, where he first met Doctor William Mayo. Doctor Mayo had been called in consultation by Henry's father, Doctor Albert Plummer. On arrival, Doctor Mayo found the elder Plummer ill and unable to accompany him to the patient's home, so young Plummer was sent in his father's place. Doctor Will was highly impressed with the keen mind of the young doctor, whose thoughts came even faster than he could express them. Driving along with his horse and buggy, Henry talked to the older doctor about chemistry, physiology and blood studies, and when they reached the patient's home, he made a microscopic demonstration showing the case to be one of leukemia.

When Doctor Mayo returned to Rochester that evening, he spoke to his brother, Charles, about the brilliant young doctor he had met. It was not long after, that Doctor Plummer became a member of the Mayo Clinic staff. In later years, Doctor Will used to say that placing Henry Plummer on the Mayo staff was the best day's work he ever did for the Clinic.

Young Plummer almost at once justified Doctor Mayo's judgment by taking charge of the clinical laboratories and by introducing modern technique and equipment. Then he turned his attention to the x-ray department and likewise reorganized that and brought it up to date.

No matter what problem he undertook, he always sought to master it from every angle by reading, questioning and experimenting. One night

when we were in his study he pointed to a physiology text and told me that he had read it several hundred times and that he really knew it by memory.

When I marveled at his great knowledge of so many things and intimated that he was a genius, he only grinned and said that whatever knowledge he had acquired had been through much hard work, and he insisted that he was not born with a larger brain than the next person. On another occasion he showed me his workshop which was filled with expensive lathes. There he would work by the hour to perfect instruments used in his esophageal work.

Doctor Plummer already had become internationally known in 1919 for his work in the development and perfection of instruments to dilate esophageal strictures and cardiospasm. It was an everyday sight to see unfortunate persons so afflicted, weak and emaciated, anxiously and hopefully awaiting their turns. I shall always remember the look of gratitude in the eyes of these patients, when, after Doctor Plummer had finished a dilatation, he would tell them to go out and eat a steak dinner. He also devised an ingenious method of demonstrating esophageal diverticula by means of the x-ray.

As the Mayo Clinic began to grow and expand, the matter of records and statistics became an ever-increasing problem. The task of setting up a new and efficient system of record keeping was assigned to the young genius, Doctor Plummer. In his characteristic manner he made a complete study of systems, travelling far and wide in search of ideas. As a result, the remarkably efficient but complex system that has since served as a model for so many other medical institutions was evolved.

Soon the Clinic became overcrowded and it became necessary to consider a new building. Naturally, the Mayo brothers assigned the task of designing their new building to Plummer. With his customary zeal and enthusiasm, he began work on the new project within a few hours. The many details that have made the Mayo Clinic such a marvelous institution in the handling of large numbers of patients are a result of Plummer's skill and knowledge in planning. The system of colored lights which directs a physician from one part of the building to another when his services as a consultant are sought by other doctors, is a brainchild of Henry Plummer. Although previous to construction of the new Clinic building, simple types of intercommunicating telephone systems had been in use, they were wholly inadequate. Doctor Plummer originated and developed a unique and complicated intercommunicating telephone system that would meet the unusual needs of the new Clinic building.

The record room where a million and a half histories are stored is a marvel of efficiency, as is the system of tubes by which histories are whisked from one department to another. If a member of the staff wishes to write a paper

on ulcer, or merely some phase of ulcer, such as hemorrhage, a remarkable mechanical system quickly places the records at his disposal. These and other ingenious devices too numerous to mention were creations of this brilliant man.

On another evening spent at the Plummer home, I was amazed to find that Doctor Plummer was a great lover of the outdoors and that he not only had an original set of Audubon's books but that he was well versed in their content. He was also familiar with the Latin names of many species of plants and flowers and knew a great deal about them. It was on this occasion that he first mentioned to me his plans to build a home in the country. He purchased a high wooded tract of land a few miles from Rochester. A stone quarry was there, so he brought masons from Italy to quarry the stone for his buildings and to construct a system of roads and a water tower. Then two large nurseries were moved to his estate. Among the many mechanical devices installed in the beautiful home, was an electrical keyboard which flashed numbers to indicate which of the numerous French doors was not securely locked. A door in the furnace opened to drop the ashes one hundred feet down into a little trolley car which would then automatically carry the ashes through a tunnel and empty them into a pit.

The flower gardens were watered by a system of sprays, all controlled by an electric button. In demonstrating this to me one day, he confided that upon surveying the grounds, he had found that the engineers were a couple of inches off in their calculations. That was Henry Plummer.

One may continue to discuss for a long time the many traits which distinguished Doctor Plummer, but a true picture of the man would not omit another side of his personality. He was truly eccentric. Once, when I saw him leave his home in town to enter his car, I called to him, hoping to get a ride to the Clinic but he was apparently so intent on driving that he failed to see or hear me. I soon realized that Plummer's mind was not on his driving but was perhaps concerned with some goiter problem, for, during the next fifteen minutes, he drove round and round the block, perfectly oblivious to everybody and everything.

When my brother, Reginald, came up to visit me one day, Doctor Plummer invited us to lunch with him at the Zumbro Hotel. We later learned that the good doctor had eaten his lunch half an hour earlier but had forgotten all about it. However, he ordered another lunch and when the waitress presented the check, my brother laid down a good sized bill and we waited for the change. When the waitress returned with Reginald's change, Doctor Plummer tipped her and pocketed the remainder.

It took my brother years to understand how Doctor Plummer could be talking intently to him on some subject and then suddenly stop in the

middle of a sentence, walk away, only to return half an hour later and continue the discussion where he had left off.

As a consultant and a teacher he was both kindly and exacting. For a long time he would not accept my blood pressure readings until he also had checked them. It was from him that I learned the importance of a carefully recorded diastolic pressure in exophthalmic goiter. He laid great stress on a low diastolic reading as a diagnostic point, since it was simulated only by aortic insufficiency.

Doctor Plummer required us to estimate the metabolic rates before turning in our reports and we were not supposed to err more than ten per cent. Probably no man has lived who possessed such a profound knowledge of the thyroid gland and its diseases. I don't know how many such cases he personally examined but I presume there must have been over 30,000.

The greatest contribution Doctor Plummer made to medical science was, of course, his discovery of the efficacy of iodine in preparing cases of exophthalmic goiter for surgery. Those of you who are old enough to remember the pre-Lugol era, recall the tragic picture of these patients, many of whom died in a crisis which no medical measure could control. Then, too, there were the patients who appeared safe for surgery, but who died following a thyroidectomy, a lobectomy, a ligation or sometimes even after an injection of hot water. One such patient, a middle-aged woman, was so frightened by the sight of a mouse that she went into a crisis and died.

We often wondered despairingly when somebody would find aid for these sufferers. Finally the answer to the problem came. There was a very sick woman in the grip of a severe crisis. She had lost twenty pounds in two weeks and was failing rapidly. Every time the Chief saw her he became more and more concerned, but could only shake his head and walk away to the next case. One day he gave orders that she was to receive 5.0 milligrams of thyroxine intravenously. Now this seemed contrary to all accepted ideas of treatment. Every professor of medicine, every medical man and every textbook, taught that iodine or its equivalent was contraindicated in this disease. That, to be sure, was just tradition; and tradition is, as I have come to believe, the enemy of progress. Contrary to all tradition, the patient did not die, nor did her condition become worse after receiving thyroxine. In a few days she passed from the crisis. You younger men probably never have seen an exophthalmic goiter patient in a crisis, for this condition has become as rare as croup, typhoid or diphtheria. I have not seen a patient in crisis in the past ten years. If correctly diagnosed in time and if given the proper treatment, no such patient should go into this state.

That incident occurred in 1921. Within a few months, Doctor Plummer was able to tell the medical world that iodine would prevent a crisis, bring a

patient out of one and so reduce the risk of surgery. Consequently, thyroidectomy could be performed with a risk of approximately 1 per cent. Yet knowledge of this great discovery was slow to spread, as Doctor Plummer seldom lectured and he wrote even less. In 1923 a paper was submitted to the *Journal of the American Medical Association* on this subject, detailing Doctor Plummer's work as well as my own results in a small series of cases. The paper was rejected on the grounds that it was too radical and was contrary to the best knowledge on the subject. In 1925, at one of the large clinics of the country, patients were still undergoing ligation operations and were not receiving Lugol's solution. That year I performed my last ligation and in 1927 I published in *Surgery, Gynecology and Obstetrics* the results of a series of 125 primary thyroidectomies. Yet so steeped in tradition were some of our best surgeons, that ligations were not entirely discontinued until the advent of the antithyroid drugs in 1945.

In the early twenties hyperthyroidism was so misunderstood that patients were often unsuccessfully treated for months as cases of intestinal disorder, heart trouble or nervous disease. Doctor Plummer's uncanny recognition of the real entity of these cases was fascinating. With his demonstration of the quadriceps test, his search for thrills and bruits, his findings of the characteristic blood pressure reading, his carefully detailed history in which emphasis was placed on weight loss and increased appetite, he would ferret out the most unusual case. Then, too, he clarified the picture for all of us who worked with him by differentiating hyperthyroidism into the two types, although this point continues to remain one of disagreement. He taught us to lay little stress on the then popular terms for the eye changes but rather to stress the points I have just enumerated.

The several years that I was more or less closely associated with Doctor Plummer as his pupil and as a member of this Association have been of inestimable value to me. The recognition that you have been good enough to give to me, is largely due to Doctor Plummer. I have always tried to express that in my writings.

In closing, I should like to quote from a letter Doctor Plummer wrote to me at the time my book, "Goiter and Other Diseases of the Thyroid Gland," was published in 1925:

"Your book was received last week at a time when I was very busy. The book went out to the house and I did not read it for a few days. However, later I got time to read it pretty well through.

"I want to congratulate you on the work. This text will prove of more service than any that has up to this time appeared. Much in most of the books has been misleading rather than of value. At this time I wish to express most sincerely my thanks for the credit you have given me in the book.

Sincerely,
H. S. Plummer, M.D."

Many fine volumes have been written on this subject since that time, several by members of this Association, which have been of great value to all of us. It is now time for some of our younger members to assume the task and to keep us up to date on the antithyroid drugs and radioactive iodine. These books could be well written by members such as Doctors Keating, Dobyns, Soley, Astwood, Bartels and others. Recently Doctors George Crile Jr., and DeCourcey published splendid books on this subject. J. H. Means' excellent book on the thyroid is really not the confessions of an elderly thyroidologist as he speaks of himself, but a treatise that should be read by all who are interested in the thyroid.

As long as diseases of the thyroid gland are talked about, any discussion will be incomplete without the name of Henry Plummer. He will always be looked upon by those who were privileged to know him as a great thinker a tremendous worker, a genius, and yet a simple, kindly, friendly sort of man, loved by his family, by his associates and by all who knew him.

Acknowledgment

I am indebted for some of the facts in this paper to the book, "The Doctors Mayo," and to Mrs. Henry S. Plummer.

CONFESSIONS OF AN ELDERLY THYROIDOLOGIST*

J. H. MEANS, M.D.

From the Massachusetts General Hospital, Boston, Mass.

A YEAR ago I had the honor of being your President. I was prevented from attending by unexpected and compulsory enrollment in an involuntary course in subjective medicine. This, I may say, was very instructive, but I deeply regretted that it conflicted with our Toronto meeting.

Dr. Crile has been so kind as to ask me to give today the address I had projected for a year ago. It is a belated Presidential address. The title, as you will perceive, is on the whimsical side. I do not really consider myself elderly, although I have been enjoying the thyroid for a relatively long time. Nor by "confessions" do I mean confessions of error only. As I read the dictionary, confessions may apply to confessions of success as well as of failure. I shall merely try to be well balanced and truthful. Finally, if anyone finds the term "thyroidology" offensive, I will plead that it is no worse than cardiology, gastro-enterology, or dozens of other ologies.

My first confession is that a gadget got me into the field of thyroidology. A passionate interest in biology originally got me into medicine, but why into the applied biology of medicine, rather than the fundamental science, I have not been able later to figure out. Probably a psychoanalysis would be necessary in order to do that.

However, I am quite clear that during my internship in 1912 I had every intention of going into the private practice of medicine as soon as I finished. My chief, the late David L. Edsall, decreed otherwise. He had become interested in the physiology of respiration and had had constructed what was then known as a Benedict Universal respiration apparatus. Having no time to use it himself, he got me a research fellowship and set me to work with it. After various explorations as to what it was good for, I settled down by 1914 to using it, primarily as a basal metabolimeter; and since alterations of basal metabolism had been shown by Magnus Levy and others to be greatest in thryoid disorders, the instrument drew me into that area.

My orientation at first was merely to use the basal metabolism as a quantitative index of thyroid function, and as such, an aid in diagnosis and

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a method of evaluating and controlling treatment. Criteria for judging the normality or abnormality of any given observed basal metabolic rate ranked high among our early objectives. On the theory that endogenous creatinine elimination is an index of total protoplasmic mass, we sought and actually found a relation between it and basal metabolism. Indeed endogenous creatinine elimination might still stand up today as a dependable point of reference for BMR if surface area had not proved more convenient and easier of application.

One of my early errors, I am sure, was to attribute too Utopian a quality to standard metabolic rate. We have since learned that considerable variation in BMR occurs within the range of normal, and that its absolute level in any subject is of less importance than are trends, upward or downward, observed over prolonged periods of time. Single determinations of metabolic rate may be no more informative than single measurements of blood pressure.

Undue preoccupation with absolute level of BMR led me in the early days to the error of believing that in the treatment of myxedema the objective should be to restore the patient's metabolism to the standard level. Now we know that the objective should be to rid the patient of symptoms with the smallest ration of thyroid that will do it. The symptoms are a better guide to treatment than the BMR.

It was in 1923 that Plummer showed that, contrary to the general belief of that day, iodine was not only not harmful in exophthalmic goiter, but specifically beneficial. I have always regretted that I took the teaching that iodine was poison to the thyrotoxic patient so uncritically. It required the genius of a Plummer to revolt from it. I can claim, however to having rapidly confirmed Plummer's findings, and to making his discovery the take-off for a long series of investigations on the nature of iodine response, and of other aspects of thyroid physiology, normal and morbid, which through the years, and largely through the cooperation of a steadily increasing number of brilliant colleagues, have become ever more fundamental in approach and objective.

By 1928 it was possible to present a fairly complete description of what iodine does and does not do in exophthalmic goiter, and to show, at least to our own satisfaction, that true refractoriness to iodine does not occur. As I have looked through the long file of publications from the Thyroid Clinic of the Massachusetts General Hospital, which is the chief way in which I prepared the present paper, among the most interesting items were the records of the spirited discussions which took place at some of the medical meetings.

One of the best of these was at the 1928 meeting of the Association of American Physicians. Plummer on that occasion talked on "the function of the thyroid gland containing adenomatous tissue." He also referred to his

famous two-product theory of thyroid secretion. I also read a paper, mine being entitled, "On the nature of the iodine reaction in exophthalmic goiter." When we had finished, the President, the late Aldred S. Warthin, unburdened himself in this wise: "As a practical pathologist, interested in the thyroid, my views are so diametrically opposed to some of the state ments made here, that I must speak of them. In Dr. Marine's views I find a sympathetic response. It is very interesting to know that we arrived at practically the same conclusions by two different routes. He has come by the experimental route, and I have come by the route of observations on human pathology and applied clinical pathology."

Dr. Warthin was referring to the famous thyroid cycle of Marine, which I think Plummer did not take much stock in. At least I can recall Plummer's saying to Marine, "You are getting the profession all mixed up on these things," or words to that effect.

Dr. Warthin went on to make two points of his own: first, that he found it extraordinary that what seemed to him to be the most important histologic change in the thyroid of exophthalmic goiter was practically never mentioned by others. He referred to the hyperplasia of lymphoid tissue of the thyroid, which he claimed constituted the most striking feature of the pathologic histology of the disease. His second point was that this histologic picture is an expression of a constitutional state of the thymicolymphatic type, which he called the Graves' constitution. Unless one were born with this, he would never get exophthalmic goiter.

I will confess that at this meeting, which I recall very vividly, I was more excited about the points on which I differed from the several speakers than by those on which we agreed. In the recorded discussions, however, I find that I did say, "The two men who have thrown more light on the thyroid problem than any others are Dr. Plummer and Dr. Marine, but these two men are very far from agreeing with each other."

At that time I was completely skeptical about Plummer's two-product theory, claiming there was no evidence for it whatever, and I think that position is still tenable today. However, for a time I went somewhat astray about hyperfunctioning thyroid tumors. I never denied their existence, but for a time I seriously questioned it. Nodular goiter with hyperthyroidism I considered to be hyperplastic goiter with incidental nodules. We now know there are such cases, but by means of radioiodine it has now been abundantly established that true hyperfunctioning thyroid tumors occur also. We have in fact, essentially three main pictures, namely, Graves' disease with diffuse hyperplasia, Graves' disease with diffuse hyperplasia and incidental nodules, and thyroids otherwise normal containing localized hyperfunctioning tumors. We call these "hot" nodules; nonfunctioning nodules we call cold nodules.

In view of these considerations I may say that I can go along with Plummer's conclusions today far better than when he uttered them. I should like to read them to you:

"1. Diffuse hypertrophy and localized hypertrophy are not, in general, part of the same disease process.

2. Exophthalmic goiter and adenomatous goiter with hyperthyroidism are distinct entities.

3. The hyperthyroidism of exophthalmic goiter is caused by hyperfunction of the entire thyroid gland.

4. It is probable that the hyperthyroidism of adenomatous goiter is caused by localized reaction in the thyroid gland, and is only an incident in the course of endemic goiter."

Warthin's remarks also make, to me, more sense—not complete sense, but more sense, now than they did when he uttered them in 1928. I should certainly agree with him that Graves' disease is a constitutional affair, and am also ready to believe that the lymphoid changes deserve some, or all, of the importance he gives them. Rawson's amazing finding that the three tissues that will inactivate thyrotropin are thyroid, thymus and lymph node, lends support to Warthin's hypothesis. As for Marine, the longer I live the more significance his whole life work has for me.

I have been trying to recall just when the thyrotropic hormone as an item of primary interest to the thyroidologist entered our thinking. In the monograph which I wrote in 1928 with E. P. Richardson, there is no mention of it. The only statement in that work which bears on this subject is where, concerning exophthalmic goiter, we say, "The relation to other endocrine glands is veiled in obscurity." Now, twenty years later, there is still plenty of obscurity, but considerable light also and very intense interest. I recall a visit to our clinic in 1931 by J. A. Schockaert of Belgium. He had just produced hyperplasia of the thyroid and exophthalmos in young ducks by treatment with anterior pituitary extracts. I believe that our steadily increasing interest in exophthalmos, its cause and treatment, dates from then. By 1934 we had Hertz and Oastler attempting to assay thyrotropin in blood and urine in thyrotoxicosis and myxedema. The blood assay was rather frustrating and remains so, but the urinary assay has been improved to the point of clinical usefulness. That the pituitary is related to Graves' disease in general, and to the opthalmopathy in particular, cannot now be doubted, but just how remains a mystery.

We encountered the pituitary again, this time rather abruptly, in 1936, when a woman entered the hospital suffering from what we thought to full blown, classic myxedema. With thyroid therapy she lost all semblance of myxedema as we had anticipated but then, to our dismay, she went into a mysterious state of shock and died. Autopsy disclosed atrophy of most of

her endocrines including the anterior pituitary and the adrenals. This is how we became conscious of pituitary myxedema, which is really a subspecies of Simmonds' disease. We have seen many cases since, and therefore must have been missing them before. However, there is no reason to miss them, if in all cases of myxedema other endocrine hypofunctions besides hypothyroidism are carefully looked for.

Since the entry of the pituitary our investigative work has been focused more and more on the activities and interrelations of thyrotropin and thyroid hormone, on the sensitivity of their end organs, and on agents which affect the balance between them. In 1929 a long series of studies with W. T. Salter began on the relation between chemical structure and physiologic activity of thyroid gland derivatives, and there is a confession concerned in that. Salter had brought back from Harington's laboratory in London, a sample of thyroxine polypeptide which he wished to have assayed in human myxedema. This was done, and it led to further studies. Among other questions, that of the effect of optical activity of thyroxine was put to the test. Harington supplied us with what were taken to be pure samples of dextro-rotary and of laevo-rotary thyroxine. When assayed in cases of myxedema these preparations had equal calorigenic activity. This seemed queer, because in general in nature laevo-rotary molecules are more active physiologically than their dextro-rotary isomers. However, we had to accept what we observed until more evidence was secured. In 1947, the experiment was repeated with new lots of material received from Harington. This time the laevo-rotary form was ten times more active than the dextro-. The interpretation accepted was that, in the first preparations, the separation of the two optically active isomers had been imperfect. It has become abundantly evident that thyroxine is the business part of the thyroid hormone molecule. Yet it also appears that when given by mouth to man, the total physiologic activity of a thyroid preparation is related more nearly to its total organic iodine than to its thyroxine iodine. I will confess that this paradox still puzzles us.

As I look back over my whole experience in the thyroid field, which now covers a period of thirty-five years, I find the story falls into fairly definite chapters. With regard to Graves' disease, there was first the pre-iodine era; then the post-iodine, and finally, the era of radioactive iodine and antithyroid drugs. All of these agents we promptly made the subject of study as soon as they were introduced.

When radioiodine came in, I predicted that it would prove an invaluable tool for research but I was dubious about its ultimate usefulness in therapy. The first part of the prediction has come true; the latter remains in doubt, not because the agent isn't effective but because we don't yet know

all we should about what its possible untoward side effects may be. I believe a very similar statement can be made about the antithyroid drugs.

Well now, I have taken up quite enough, if not too much, of your time with this sort of reminiscence. I shall close with one final confession—a confession of faith this time—faith in this Society.

Its intellectual growth has been steady; its development sound. I predict that as the years go by it will continue to increase in usefulness. The reason I believe this is because its angle of approach to the problems which interest us all is constantly widening. As is true today in any branch of science, so in thyroidology, it is necessary to bring many skills to bear upon the major problems in the field if there is a real will to solve them. In our Society the surgeon, physician, pathologist, physiologist, biochemist, and now the biophysicist and others, all get together to help one another in our meetings.

I place a high value on my membership, as I am sure we all do.

HASHIMOTO'S DISEASE*

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IN the past few years we have seen an increasing number of goiters which are classified as Hashimoto's type of chronic thyroiditis. We want to bring this to your attention, along with several other observations we have made in the 28 cases of the disease seen from 1935 to the present time. All but 2 of these cases were encountered since January, 1943.

In 1912 Hashimoto (1) described "struma lymphomatosa," which differed from other forms of chronic thyroiditis and especially from Riedel's (2, 3, 4) "eisenharte struma." Since that time there has been considerable controversy as to whether they actually are different processes.

In 1922 Ewing (5) studied 4 cases and concluded that Hashimoto had described the early, and Riedel the late stages of the same process. Others who take this same view include Boyden, Coller and Brugher (6), Perman and Wahlgren (7), Williamson and Pearse (8), Heyd (9), Eisen (10), Womach (11), Reist (12), and Shaw and Smith (13). In 1931 Graham and McCullagh (14) gave impressive support to the belief that these are two separate types of thyroiditis. McClintock (15), and Scarello (16), have shown that the tissue of the thyroid did not change from the Hashimoto type toward the Riedel type, but remained the same, judging from biopsy specimens taken two and thirteen years later respectively. Lee (17), Joll (18), Heineke (19), Moore and Lloyd (20), Lee and McGrath (21), Poer, Davison and Bishop (22), McSwain and Moore (23), and Decourcy (24), join the ranks of the separate entity followers. DeCourcy (25), furthermore, suggests that it is possible to have both processes in the same gland simultaneously.

CLINICAL MATERIAL

Struma lymphomatosa is not a respecter of geographic or social boundaries, and is found very predominantly among females. None of our cases was in a male and we have noted only 8 reports in the literature in which Hashimoto's disease was found in the male.

The average age of the patients as given in the literature by various authors varies from 43.8 years (26) to 57.6 years (18), the youngest being

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10 and the oldest 78 (17). In our series the youngest was 14 and the oldest 62, with an average of 37.7 years (Table 1).

All but one of the patients in our series had noted her goiter for varying lengths of time, some since girlhood. All of them were or had been nervous and gave a history of having some emotional unrest in the past. Seventeen complained of choking or difficulty in swallowing, and 18 had palpitation of the heart. The basal metabolic rate ranged from minus 5 to plus 50 per cent, the average being plus 14 per cent. The basal metabolism was not determined in every patient but, in general, only in those who appeared thyrotoxic. The serum cholesterol varied from 125 to 250 milligrams per cent. The thyroid gland was usually described as being diffusely enlarged, rather firm and having a pebbly feel. The upper poles of the gland were usually a little broader than normal and, as Cattell (27) described it, "more like the gland of the exophthalmic goiter that had been treated with iodine."

At operation the thyroid gland was usually uniformly involved. In 2 instances in our series the disease was not diagnosed at the operating table and it was thought that the rest of the gland was normal but no biopsy of the remaining gland was made. There were no adhesions between the gland and the surrounding tissue, except possibly the trachea. The color of the cut surface of the gland varied, but was usually a lavender-tinted yellow. Upon clamping the gland the clamp usually tended to cut through it, clinging only to the blood vessels and strands of fibrous tissue. Usually a small amount of clear fluid could be pressed from the gland. The blood supply was probably slightly less than normal.

Microscopically there was an acidophilic degeneration of the thyroid epithelium with replacement by lymphocytes and fibrous tissue. The lymphoid tissue, which usually predominated, was often in the form of numerous follicles.

Little is actually known of the *etiology* of Hashimoto's disease. It is certainly not any part of the acute inflammatory process, although Brunger (28) and Eason (29) regard the presence of the lymphoid follicles as evidence of inflammatory reaction. Simmonds (30) describes changes in the thyroid glands resembling Hashimoto's disease in obese elderly individuals. Some authors (12, 31) believe that iodine therapy may have some relationship to it. Graham (32) does not exclude the relationship of lymphosarcoma, for he believes he has seen a case which exhibited such transition. Patterson and Starkey (26) have also reported such a case. Williamson and Pearse (8) believe that it is a subnormal gland undergoing compensatory hypertrophy. McCarrison (33) has produced a picture simulating lymphadenoid goiter in the rat by means of an iodine-containing, vitamin-deficient diet. DeCourcy (24) has shown that Riedel's struma is preceded by a perithyroiditis, causing an ischemia of the gland. There is no such

process in Hashimoto's disease except that in some instances the lesion inside the gland may give rise to a perithyroiditis secondarily. Jaffe (34) found that some thyroids at autopsy, although not enlarged, showed Hashimoto-like changes with thick walled arteries and arterioles. Bohan (35) reports isolation of an organism found in dental infection which, when injected into the rabbit, caused Hashimoto-like changes in the thyroid. Shaw and Smith (13) report adrenal lesions like those in the thyroid gland of Hashimoto's disease. It is interesting to note that all of our patients claim to have had some emotional upset prior to the onset of the goiter. We should like to stress that this is a younger group of patients than that reported previously in the literature and that they were encountered since 1943—two years after our entry into World War II. A large majority of these patients had husbands, sons, or sweethearts in the service and were thus subject to anxiety. This constant anxiety and chronic emotional unrest may have resulted in chronic stimulation of the thyroid gland, causing an increase in all types of goiter, including Hashimoto's disease.

There is considerable controversy as to the correct *treatment* of this condition. All of our patients have had either subtotal or total thyroidectomies. In order to analyze our results following the surgical treatment of Hashimoto's disease we shall first define our postoperative conditions. To make the diagnosis of myxedema we have followed Thompson's (36) description. This diagnosis was not made unless there was puffiness of the face, hands or eyelids, or a significant gain in weight. The patient may also have swelling of the tongue and larynx with a slow, slurred speech, dryness of the skin and hair, and alopecia. A diagnosis of hypothyroidism depended upon the presence of fatigue, lowered blood pressure, intolerance to cold weather, a decrease in the basal metabolic rate or an increase in the serum cholesterol. Twenty-eight of these patients have been followed and 9 have developed myxedema (32.3 per cent). Of the 13 patients who had total thyroidectomies 8 developed myxedema (61.5 per cent), whereas of the 15 who had subtotal thyroidectomies only 1 developed myxedema (6.7 per cent). This is a somewhat lower incidence of myxedema than that reported in the literature. Joll (18) reports 64.8 per cent and McClintock and Wright (15), 78.8 per cent. We wonder if these authors were not using the terms hypothyroidism and myxedema synonymously. Twenty-five of the 28 patients developed hypothyroidism (89.3 per cent). The average postoperative basal metabolic rate, performed at least six months after operation, was minus 7 per cent and the average serum cholesterol was 252.8 mg. per cent. Two patients are at present in a state of euthyroidism, one after total thyroidectomy and one after subtotal thyroidectomy. We have not treated any of our patients with x-radiation as advocated by Renton

TABLE 1. SUMMARY OF 28 CASES OF HASHIMOTO'S DISEASE (STRUMA LYMPHOMATOSA)

Patient	Age (yrs.)	Preoperative		Type of thyroidectomy		Postoperative follow-up			
						Myxedema			
		B.M.R. %	Serum cholesterol (mg. %)	Subtotal	Total	Yes	No	B.M.R. %	Serum cholesterol (mg. %)
E.T.	32	+22		√			√	+18	272
K.T.	14			√			√		245
P.L.B.	38	− 1		√			√		
F.H.	33			√			√		247
J.H.M.	53			√			√		
J.S.J.	54				√		√	− 7	212
F.H.	54	− 5	214	√			√		
W.E.F.	36	+44	125		√	√		−27	322
W.L.J.	29				√		√	−20	347
F.M.	43	+ 4	227		√	√		+20	162*
G.R.F.	30			√			√	− 2	157
W.F.P.	45	+17			√	√			
R.S.K.	42		230	√			√	−10	222
J.M.K.	22				√	√			
P.H.	26				√	√		− 3	254
W.T.F.	27		250	√			√	−18	285
L.H.C.	48	+19		√		√			
M.J.	27	+16	207	√			√		270
L.E.W.	37		181	√			√		
T.W.M.	32	+ 9	180	√			√	− 9	175
E.B.	27	0	160		√	√		−11	380
A.B.C.	57	+50	153		√	√		+18*	300
J.L.C.	35	− 3		√			√		
M.R.†	32				√		√		
O.B.‡	62				√	√			
L.S.§	50				√		√		
S.E.R.#	31			√			√		
B.H.‡	30				√		√		
Average	*37.7*	*+14*						*−7*	*252.8*

* Taking desiccated thyroid.
† Patient of Dr. B. L. Shackleford.
‡ Patients of Dr. W. A. Kelley.
§ Patient of Dr. H. E. Steadman.
# Patient of Dr. B. H. Clifton.

et al. (37), who claim that they have one patient who shows no hypothyroidism after five years. Others who agree about x-ray treatment are Means (38), Schilling (39) and George Crile, Jr. (40), but Boyden, Coller and Brugher (6), and Marshall, Meissner and Smith (41) do not use it because they feel that it may further reduce the amount of thyroid secretion. McSwain and Moore (23), however, state that the incidence of hypothyroidism after x-ray therapy is not as high as after operative procedures.

In 1934 Polowe (42) reported a case of Hashimoto's disease in which the B.M.R. was plus 43 per cent and it was discussed at the meeting of the American Association for the Study of Goiter in 1940. Crane (53) and later Polowe (42) and Womach (11) proposed that hyperthyroidism was the first sign of Hashimoto's disease. In view of the microscopic picture and the fact that our patients were of a younger average age than those previously reported and had higher basal metabolic rates, we feel that we have been dealing with many early cases. We are inclined to agree that in the early stages of Hashimoto's disease there is a slight hyperthyroidism, followed by euthyroidism and then hypothyroidism.

SUMMARY

Twenty-eight cases of Hashimoto's disease seen since 1935 are reported. Twenty-six of these cases were seen since 1943.

The average age of these patients was less than that previously reported in the literature, and the preoperative basal metabolism was higher.

Following total thyroidectomy, mild myxedema developed in 61.5 per cent of the patients; whereas, following subtotal thyroidectomy, it developed in only 6.7 per cent of the patients. Hypothyroidism occurred in 89.3 per cent of the total number of cases.

A review of the theories concerning the etiology of the disease is presented.

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MEDIASTINAL EMPHYSEMA AND PNEUMOTHORAX FOLLOWING THYROIDECTOMY. REPORT OF TWO CASES*

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MEDIASTINAL emphysema with pneumothorax, unilateral or bilateral, is an uncommon complication following thyroidectomy but it is a definite possiblity and undoubtedly occurs more frequently than recognized. Of 16 instances reported in the literature, 11 patients died. This mortality is much higher than one would expect from such a complication and would lead one to believe that it occurs more often in an unrecognized and less lethal form. The symptoms, which are primarily those of a tension pneumothorax, appear during or soon after the operation and may lead to death so quickly that the surgeon does not have the time to analyze the situation or even gather together sufficient information from which to make a diagnosis. Furthermore, unless the postmortem pathologist routinely takes premortem roentgenograms of the chest or makes special efforts to rule out pneumothorax, the condition will not be recognized even at the autopsy table. If the autopsy is delayed a number of hours, air in the mediastinum diffuses and may not be discovered. The clinical diagnosis however is not a difficult one to make, providing the surgeon has knowledge of the possibility of its occurrence. This is well exemplified in the following two case reports. The first one, in which the patient developed a mediastinal emphysema with a bilateral pneumothorax a few hours after operation, brought to my attention for the first time the possibility of such a complication. In the second one, symptoms of an alarming nature appeared immediately following operation and would certainly have resulted in death if the intrathoracic tension had not been relieved.

Case 1: This patient was a male, aged 48. During the preceding year he had three attacks of rapid and irregular heart beat. A physician observed him during two of these attacks and diagnosed the irregularity as auricular fibrillation. There were no other symptoms. He had a bilateral nodular goiter, each lobe being about the size of a hen's egg. The roentgenogram of the chest was normal. The basal metabolic rates were minus 18 per cent and minus 12 per cent. The diagnosis was nontoxic nodular goiter and thy-

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roidectomy was advised: 1) merely to remove the lumps, and 2) because of attacks of auricular fibrillation.

February 17, 1947: Bilateral subtotal thyroidectomy was done under ethylene and oxygen anesthesia without an intratracheal catheter. The anesthesia was begun at 8:30 and terminated at 9:40 a.m. There was no difficulty with the anesthesia and the blood pressure, pulse rate and respiratory rate were within the usual normal limits throughout the operation. The patient had an ordinary bilateral multiple nodular goiter.

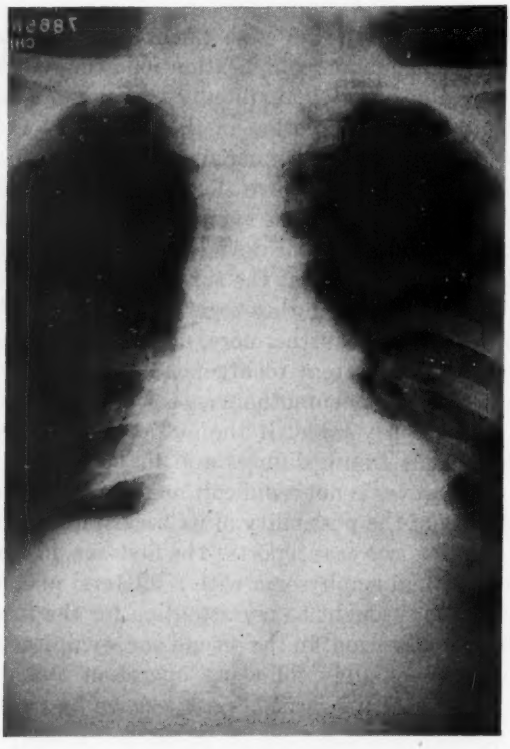

FIG. 1. Case 1. Massive bilateral pneumothorax with mediastinal and subcutaneous emphysema, five hours after thyroidectomy.

The removed lobes weighed 114 grams. The operative procedure was uneventful. The inferior thyroid artery was ligated proximally on the right side and the recurrent laryngeal nerve was visualized on that side. A small Penrose drain was left in the wound.

The patient was returned to his room awake and in good condition. At 1 p.m. he complained of severe pain in the left side of his chest and difficulty in breathing. The respiratory rate rose to 28 per minute and the pulse rate from 90 to 130. He was immediately placed in an oxygen tent. It was thought that he had a massive collapse of the lung.

A roentgenogram (Fig. 1) at 1:45 p.m. showed a bilateral pneumothorax of at least 50 per cent on each side and emphysema in the mediastinum and in the soft tissues of the neck and shoulders. At 9:30 p.m. 1500 cc. of air was aspirated from the right pleural cavity and 1900 cc. from the left. He was much relieved.

February 18, 1947: In the morning he was out of the oxygen tent and was reasonably comfortable. A roentgenogram of the chest showed some re-expansion of the lung and less emphysema in the soft tissues. At 4:00 p.m. he again complained of severe pain in the chest, the pulse became weak, the rate rose to 130 and the respiratory rate to 28. A second x-ray film was approximately the same as the one taken in the morning but the subcutaneous emphysema about the neck had increased somewhat. A needle was inserted into the pleural cavity through the second interspace anteriorly on each side and connected by rubber tubing to an exit through a glass tube under water. He was relieved of most of his distress. During the night his heart became irregular and continued this way for several hours.

February 19, 1947: An x-ray film of the chest revealed excellent expansion of the lungs and in the afternoon both needles were removed. He was out of bed the next day and made an uneventful recovery, apparently none the worse for the experience.

Case 2: This patient was a man, aged 36. During the fall of 1947 he developed symptoms of exophthalmic goiter. He lost 17 pounds in weight with a good appetite, became nervous, had a tremor, heat intolerance, palpitation and rapid heart beat, a diffuse enlargement of the thyroid gland to about twice the normal size and a moderate exophthalmos. The basal metabolic rate was plus 34 per cent. In December, 1947, the administration of 150 milligrams of propylthiouracil daily and 10 drops of Lugol's solution three times daily, was started. The symptoms were completely controlled. This therapy was continued until September, 1948—nine months, at which time the basal metabolic rate was plus ten per cent. Treatment was then discontinued. Symptoms recurred after one month. In October the same therapy was resumed, except that the propylthiouracil was increased to 200 milligrams daily. The treatment again controlled the symptoms completely and was continued for three more months, at which time a thyroidectomy was performed.

January 29, 1949: Subtotal resection of both lobes was done. The goiter was diffusely hyperplastic, about twice normal size and rather friable. The operative procedure itself was uneventful. Both inferior thyroid arteries were ligated proximally and both recurrent laryngeal nerves were visualized. During the operation there was no notable difficulty in breathing. This patient, as well as the first one, was permitted to waken partially and forced to strain before the wound was closed; the anesthesia was then reinstituted. Ethylene and oxygen inhalation anesthesia was used without an intratracheal tube. The anesthesia was begun at 7:55 a.m. and terminated at 9:30 a.m. At the beginning of the operation the blood pressure rose to 210–220 systolic and 70–80 diastolic and continued at these levels for twenty minutes: then it dropped to 180–190 systolic and 70 diastolic, where it remained throughout the rest of the operation. The pulse rate at the onset was 130 per minute but dropped to around 100–110. The respiratory rate rose immediately and varied between 30 to 40 per minute during the entire precedure. No significance was attached to the increased respiratory rate although in view of subsequent events it may have been significant. The patient did not awaken from the anesthesia. At 10:00 a.m., a half hour after the operation, he was comatose, cyanotic and breathing at an exceedingly rapid rate—50 to 60 per minute. When oxygen was administered through a gas mask continuously for a few moments he had a typical tetanic carpopedal spasm. The tetany undoubtedly was due to alkalosis from the washing away

of carbon dioxide from the lungs. There was no subsequent evidence of a parathyroid deficiency.

It was noted that the respirations consisted of a long expiratory phase and a very short, almost instantaneous, inspiratory phase. From the character of the breathing it was suspected that he had a tension pneumothorax. On examination of the chest it seemed that the left side was more resonant and that the breath sounds were much less distinct. A roentgenogram (Fig. 2) taken at 10:30 a.m., one hour after operation, re-

FIG. 2. Case 2. Almost complete left pneumothorax, one hour after thyroidectomy.

vealed a large left pneumothorax and mediastinal and subcutaneous emphysema. The subcutaneous emphysema was never marked. It could not be seen on inspection but could be felt by palpation above each clavicle.

A needle was inserted anteriorly through the chest wall in the second interspace. A considerable quantity of air was withdrawn but it was not measured and the needle then was connected to a water-seal bottle. The patient's condition improved rather slowly. It was several hours before he regained a reasonable degree of consciousness. Cyanosis and dyspnea persisted in a lesser degree but sufficient to necessitate continuous

enclosure in an oxygen tent. Air bubbled out continuously from the end of the underwater tube.

January 30, 1949: Dyspnea was still present but was much less severe. A roentgenogram showed the lung to be well expanded. At 1 p.m. the thoracic needle was removed and the patient was transferred from the oxygen tent. Later in the afternoon he had an attack of pain in the left side of the chest, became very short of breath and oxygen therapy was reinstituted.

January 31, 1949: A roentgenogram showed left hydropneumothorax and the needle was reinserted. Air was expelled through the apparatus for three more days, during which time it was necessary to keep him almost continuously in an oxygen atmosphere.

February 2, 1949: The apparatus was intermittently ineffective and an x-ray film revealed again a large pneumothorax.

February 4, 1949: No more air could be expelled from the chest. The patient could tolerate removal from the oxygen tent. One hundred thousand units of penicillin G in aqueous solution was injected through the needle and the latter was removed.

February 6, 1949: A roentgenogram showed the chest to be normal, with no evidence of the previous disturbance. The patient promptly recovered without further trouble and without any discernible harmful after-effects. The wound healed unusually well. A Penrose drain was removed on the fourth day. At no time was air observed to pass in or out of the wound.

DISCUSSION

Incidence: Mediastinal emphysema (ME) and pneumothorax (PT) probably have an identical origin and are considered as parts of the same entity. Keis (1) in 1934 reported a case of ME and PT following a thyroidectomy and found 7 more in the literature. I was able to find the references to only 6, as follows: Jehn and Nissen (2), one case; Gold (3) four cases; and Buford (4) one case. Since then 8 more have been reported: Barrie (5) three cases; and Adams (6), Billimoria (7), Herrmann (8), Meek (9) and Seidl (10), one case apiece. In addition, Blumel (11) reported a case of ME following ligation of all four thyroid vessels. Out of the 16 reported cases there were 11 deaths. Bilateral PT was found ten times and ME without mention of PT, twice. In most of the cases there was associated subcutaneous emphysema about the neck. Symptoms appeared either during the operation or a few hours thereafter. In over half the cases difficulty in breathing was noted, either as the result of removing an intrathoracic goiter or as a result of trouble with the anesthesia.

Meek (9) reviewed 21,869 thyroidectomies reported in the literature and found no mention of the complication. Pemberton, in a personal communication said that he knew of none occurring at the Mayo Clinic. Billimoria (7) stated that Sir Thomas Dunhill and Mr. C. A. Joll, both of whom have performed a large number of thyroidectomies, never saw it. This postoperative complication is by no means peculiar to thyroidectomy. It occurs by far the most often following tracheotomy for obstructive dyspnea, in which it reaches an incidence of as high as 41 per cent (12).

Although of rare occurrence following a thyroidectomy, it has its next highest incidence following this operation. It has been reported following gastric resections (13, 14, 15, 16, 17), other operations on the neck such as gland resections (18), ligation of the jugular vein (4, 19), operations on the stellate ganglion (20) and esophagus (8), choledochostomy (21), appendectomy (22), tendon transplant (23), tonsillectomy (24, 25), kidney operations (26, 27, 28) and following anesthesia alone (29). The condition, of course, occurs in otherwise apparently healthy individuals (30, 31, 32) and in a varied assortment of disorders, most of which are associated with overinflation of the lung, either local or general (33, 34). It perhaps reaches its highest incidence in newborn babies. Davis (35) in a routine radiographic check in 702 newborn infants found PT six times.

Etiology: There are five conceivable pathways by which air might enter the pleural cavity. These are listed in the order of increasing probability as follows:

1. Through a tear in the apical pleura.
2. Through a break in the tracheal walls into the mediastinum and thence into the pleural cavity.
3. By way of a ruptured bleb on the lung surface.
4. By the sucking of air into the mediastinum through the open wound in the neck and thence into the pleural cavity.
5. By the rupture of an intrapulmonary vesicle with passage of air along the vascular sheaths through the root of the lung into the mediastinum and thence into the pleural cavity and the subcutaneous tissues of the neck.

The first two of these possibilities, *i.e.*, injury to the trachea or to the apical pleura, can be dismissed. No injury to the trachea has been noted either on the operating table or on the autopsy table. Damage to the pleura is anatomically unlikely and damage to both pleural surfaces very unlikely indeed. In the 10 patients upon whom postmortem examinations were performed, no injury to the parietal pleura was found.

The most frequent explanation given as the cause of ME and PT following thyroidectomy, is the sucking of air through the open wound into the mediastinum and thence into the pleural cavities. Joannides and Tsoulos (36) demonstrated clearly that when air is forced into the mediastinum under pressure it bubbles through the thin pleural surfaces of the mediastinum into the pleural cavity. This was verified in cadavers by Keis (1) and Barrie (5). Goldberg, Mitchell and Angrist (37) injected air under the deep cervical fascia in 9 cadavers, all under one year of age. At pressures of 40 mm. of mercury the air would rupture into the pleural cavity, after which much more air would enter at pressures of 0–5 mm. of mercury. By routine postoperative roentgenograms following tracheotomy they found

ME in 12 of 18 cases and are of the opinion that the air enters through the neck. Neffson (38) found PT and ME in 17 out of 126 tracheotomies. Forbes *et al.* (12) found ME after tracheotomy in 30 (41 per cent) of 71 patients checked by x-ray examination and PT in 12 (15 per cent) of 82 patients. There were two deaths from this cause alone in a total of 120 tracheotomies. This high incidence of ME and PT following tracheotomy would tend to confirm the theory that the air reaches the pleural cavity by way of the neck. Yet Figi (39) reported 200 tracheotomies and did not mention the complication at all. His patients differed from those of the other authors in two respects: a) they were mostly adults, whereas the others were children, and b) the tracheotomies were not as rule performed as emergency procedures for severe obstruction, as in the case of the others. Analysis by Neffson (38) and Forbes (12) indicated that ME and PT increase in incidence with the severity of obstructive symptoms. Most of the cases of ME and PT reported following thyroidectomy were in patients also exhibiting evidence of respiratory obstruction during the course of the operation. Seidl (10), much as did Goldberg (37), injected air into the dog's mediastinum through a glass tube. He found that with 100 cc. of air there was no change; at 300 cc., no change; but with 600 to 800 cc., with pressures of plus 22 to plus 26 cm. of water, there was a sudden drop of pressure to minus 8 to 10 cm. when air entered the pleural cavity. In a patient with an intrathoracic goiter he found a mediastinal pressure of 0 to minus 3 cm. of water in ordinary breathing and from minus 8 and minus 10 cm. to plus 2 and plus 4 cm. on deep breathing. In three patients with an outspoken intrathoracic goiter be found no evidence of ME by x-ray examination four hours postoperatively. He could not obtain in animals any pressure rise in the mediastinum by the simple sucking in of air. Although he admits the possibility of air being sucked into the mediastinum, he cannot conceive of sufficient pressure being built up to cause its rupture into the pleural cavity. In his opinion, if air entered the mediastinum by this route it should be absorbed or even come out of the wound or through the drainage opening. Indeed, the surgical treatment of severe ME is an incision above the sternal notch to permit the exit of air. In the second case reported here, very large quantities of air were withdrawn from the chest over a period of three days during which time the wound, although it contained a small latex rubber (Penrose) drain, was sealed over and certainly could not have given ingress to such a large volume of air. Similar circumstances led Adams (6) to a similar conclusion. Obviously, this hypothesis for the explanation of the condition following neck operations could not be applied to abdominal and other operative procedures.

The rupture of an emphysematous bleb with a valvular flap on the surface of the lung is a commonly accepted explanation for spontaneous PT.

Kjaergaard (40) demonstrated such a valve vesicle in one autopsy and possibly in a second but most pathologists search for them in vain. It must be admitted, however, that the openings through which air seeps from the mediastinum into the pleural cavity are also not discernible to the post-mortem pathologist. But much higher pressures are required to rupture the normal visceral pleura than the thin mediastinal pleura. It is undoubtedly possible for PT to result from this cause but it does not seem possible that the PT thus produced would result in mediastinal and subcutaneous emphysema. Although air passes rather easily from the mediastinum into the pleural cavity it cannot be forced under ordinary pressures from the pleural cavity into the mediastinum. In Adams' case (6) the patient had asthma plus emphysematous lungs as proven by preoperative x-ray examination. This is the only case reported in the literature in which there was any abnormality of the lung itself. His patient had a right tension PT, apparently without mediastinal or subcutaneous emphysema. No autopsy was performed. That the PT arose from a ruptured vesicle is unquestionably possible. Yet Peterson (41) reported a death from ME and PT in asthma and collected 7 from the literature, in all of which there was associated ME. The presence of ME is in itself presumptive evidence that in these cases the air passed from the mediastinum into the pleural cavity rather than the reverse.

Macklin and Macklin (42) have recently made an exhaustive review of ME and PT with an interpretation of the clinical literature in the light of laboratory experiments. From it one can obtain practically all the useful information that there is on the subject. It is their contention that the syndrome of PT, ME and subcutaneous emphysema begins as a pulmonary interstitial emphysema due to the rupture of intrapulmonary vesicles. As a result of local or general hyperinflation, air ruptures through the vesicles based on the sheaths of small branches of the pulmonary vessels. It makes its way along the vessel sheaths to the mediastinum. It may then make its way upward into the neck or downward along the aorta and esophagus. It may rupture the mediastinal wall producing pneumothorax. Once the leakage has begun, the pressure necessary to continue the leak need not be so high as that initiating the rupture. In some patients, the air builds up sufficient pressure within the lung itself to block off the pulmonary circulation and even bronchoalveolar ventilation. In some, it builds up dangerous pressure within the mediastinum. In some, the air passes upward into the neck with relief of mediastinal pressure. In some, it ruptures into one or both pleural cavities with or without tension pneumothorax. The path it will take is not always the same and is not predictable. This theory will satisfactorily explain the history and findings of all the reported cases of ME and PT following thyroidectomy. No other one will.

Diagnosis: The diagnosis depends primarily on the surgeon's awareness of the possibility. The catastrophe may arise during, or a few hours after the operation. The first intimation is usually dyspnea and cyanosis but in some instances it may be subcutaneous emphysema about the neck. Tension pneumothorax is the common cause of death. When it occurs, the rapid breathing is characterized by a relatively long expiratory phase with an exceedingly short inspiratory phase. Since the patient no longer can produce negative pressure in the pleural cavity he breathes by compressing the lung in a forceful expiratory effort; the sudden elastic recoil of the chest wall produces a very temporary negative pressure permitting the ingress of a small quantity of air. The patient breathes so rapidly however that the difference in expiratory and inspiratory phase is not discernible to the observer unless he himself breathes synchronously with the patient. This maneuver alone will almost immediately spot the dyspnea as being due to a tension pneumothorax. Since subcutaneous emphysema is almost a constant accompaniment of the condition a careful examination of the neck for subcutaneous air will immediately indicate the true state of affairs. This physical sign, sufficient in itself to suggest the diagnosis, was overlooked in both of our cases. A tympanitic percussion note and absence of breath sounds will be found on the affected side. If air has seeped into the pericardium, there will be a crunching or crackling sound with each beat of the heart. If the tension PT is on the left side, the enfeebled heart sounds may not be heard and there will be changes in the electrocardiogram due to displacement of the heart. The pressure of air in the mediastinum and the lung itself causes a reduction in the return flow of blood to the heart with a consequent drop in blood pressure.

A roentgenogram of the chest readily establishes the diagnosis of PT but ME is not so easily recognizable. On the antero-posterior view, air in the mediastinum causes a widening of the mediastinal shadow and marks it with irregular longitudinal dark streaks (Fig. 1 and Fig. 2). A lateral exposure is much better for diagnostic purposes and is necessary before one can rule out the presence of ME but a lateral view is almost impossible to obtain on a dyspneic bed patient by means of a portable x-ray machine.

Treatment: If tension PT is present, a large needle is inserted into the pleural cavity in the affected side through the second interspace in the midclavicular line. Air is withdrawn. One end of a rubber tube is attached to the needle and the other end kept under water, preferably by attaching it in turn to a glass tube in the usual water-seal bottle so that variations in negative and positive pressure can be observed. If the needle is passed through a cork, the latter can be fixed to the skin in order to hold the needle in position. Since the complication has been assumed to be due to air being drawn through the wound, it has been recommended that all drains be

removed from the neck. It would seem more logical that the wound be opened widely! Relief of the pneumothorax does not always completely relieve the dyspnea. The first patient, with a rather extensive bilateral PT, was almost completely relieved of his distress by aspiration of the contained air but the second patient, with only a unilateral PT of a lesser severity, had to be kept in an oxygen tent for almost three full days. During this time the PT alone could not account for his dyspnea and cyanosis when out of the oxygen tent. It is very likely, as pointed out by Macklin, that the air in the mediastinum produced an air block which prevented the return flow of blood to the heart and that his dyspnea was primarily due to the ME rather than the PT.

SUMMARY AND CONCLUSIONS

1. Two cases of mediastinal emphysema and pneumothorax are reported following thyroidectomy.

2. Sixteen cases have been reported in the literature with 11 deaths. It is probable that the complication has occurred much more frequently, at times being unrecognized and followed by recovery and at times being unrecognized even at autopsy.

3. The complication follows many other operative procedures. It is very common after tracheotomies for obstructive dyspnea. It is uncommon following thyroidectomy but apparently has its next highest incidence after this operation.

4. It is most likely the result of rupture of an intrapulmonary vesicle with the passage of air along the vascular sheaths into the mediastinum and thence into the pleural cavity and neck.

5. The diagnosis is not difficult, providing the surgeon is aware of its possibility. If recognized, the condition is nearly always remediable. If not recognized, it may easily result in death.

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SURGICAL TREATMENT OF HYPERTHYROIDISM*

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SUBTOTAL thyroidectomy has been conclusively demonstrated to be effective in the treatment of hyperthyroidism, both for the adenomatous or nodular type and for the primary or diffuse toxic type. In experienced hands, the operation can be performed with an operative mortality of 1 per cent or less and with few complications. Furthermore, satisfactory results are achieved in 90 to 95 per cent. The operation, as carried out today, has reached a high state of perfection but such has not always been the case. Indeed, the high incidence of complications which has been reported in earlier series, including an appreciable number of recurrences of the disease, has frequently been quoted in the literature as reason to employ an operation only as a last resort after failure to control symptoms by so-called conservative measures. That such a situation should not exist today will be pointed out in this presentation, which will review experiences at the Lahey Clinic in the surgical treatment of 1,000 consecutive cases.

The employment of thyroidectomy in the treatment of hyperthyroidism can properly be divided into three periods. The first might be termed the pre-iodine era, *i.e.*, previous to 1923. During this time operation was hazardous and surgery was performed under difficult circumstances, yet technical methods were developed which formed the basis for the present-day operation of subtotal thyroidectomy. The second period, from 1923 to 1943, can be considered the iodine era, during which time iodine was used in the preoperative preparation of patients. This led to a marked reduction in surgical mortality and postoperative complications. During this entire period the operation of subtotal thyroidectomy was greatly improved and became more effective. The third period, since 1943, following the introduction of the antithyroid drugs has again modified the treatment of hyperthyroidism. This discussion will be limited to the last period.

During the six-year period, May 1943 until May 1949, 1,630 patients with hyperthyroidism have been prepared for subtotal thyroidectomy by the use of antithyroid drugs. This paper will consider the first 1,000 patients. Although five different preparations have been used, propylthioura-

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cil has been the drug of choice in most cases. The routine preoperative preparation of patients by the antithyroid drugs is supplemented by the administration of iodine during the last two or three weeks of the treatment. Early in the six-year period, an appreciable number of patients with hyperthyroidism continued to be prepared with iodine alone but this preparation was chiefly confined to the milder cases and more recently the number so prepared has been small.

In reporting this experience it is important to realize that the surgery has been performed by nine different surgeons and represents their combined experience during this six-year period. The preoperative preparation of these patients has been under the direction of the medical department of the clinic, chiefly in the hands of Dr. Elmer C. Bartels and Dr. George O. Bell. Detailed information relative to all cases both before and after operation has been kept by Dr. Bartels and Dr. Bell, and I am indebted to them for many of the detailed figures. During the six-year period there has been no selection of cases, so that mild and severe cases are included as well as all of the poor risks. Fourteen per cent of the patients fell in a group known as thyrocardiacs and among the total was an appreciable number of children under 13 years of age and patients with diabetes mellitus.

Advantages of the surgical treatment of hyperthyroidism

There are many reasons why thyroidectomy should be employed in the treatment of patients with hyperthyroidism. Operation has had a long period of trial and has proved to be very effective. Many follow-up studies have been made which demonstrate that the relief of symptoms is maintained permanently in 90 to 95 per cent of patients. Operation can be carried out with a low mortality and with few complications. The evidence so far indicates that it probably results in the relief of more of the symptoms and signs of the condition than any other method and is probably essential in most diffuse nodular goiters complicated by hyperthyroidism. It possesses a great advantage when large numbers of patients apply for treatment, as is the case in our Clinic where approximately 500 new patients with hyperthyroidism undergo treatment each year. At the present time only a five- or six-day total hospital stay is required and most patients are able to return to work in a period of two to four weeks after operation. Thyroidectomy offers a rapid and predictable result. Based on our experience in the treatment of a large number of patients with hyperthyroidism, we consider it the best method for treatment.

Preparation with antithyroid drugs: effect on subsequent thyroidectomy

Without any question, the technical difficulties of thyroidectomy are increased when patients have been prepared with the antithyroid drugs. In our earlier experience the gland was found to have a greatly increased

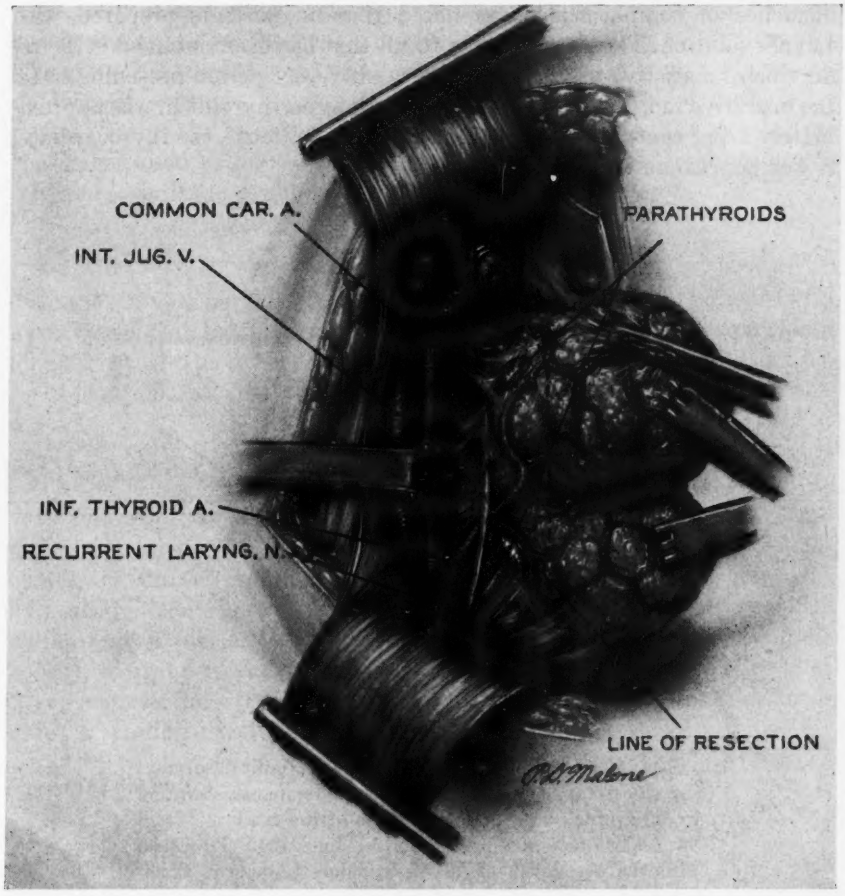

FIG. 1. The superior thyroid vessels have been doubly ligated and divided. The superior and inferior parathyroids have been identified. The recurrent laryngeal nerve is demonstrated for its entire cervical course. The inferior thyroid artery will then be ligated in continuity. (From Surgical Clinics of North America, June 1949. Published with the permission of W. B. Saunders Company, Philadelphia.)

vascularity and to be very friable. The appearance of the gland was not unlike that observed in patients before the use of iodine. Most of these technical difficulties have been overcome by causing involution of the gland by the administration of iodine during the latter part of the preoperative period but it still remains necessary to exercise the greatest care in carrying out the procedure, in order to avoid the complications that may follow thyroidectomy. This became evident soon after the employment of the antithyroid drugs when, as reported in an earlier review, a higher

incidence of complications was noted than in patients prepared with Lugol's solution. The most striking result that has been obtained is the reduction of operative mortality. In the twenty-year period preceding 1943, the operative mortality for all patients with hyperthyroidism was approximately 1 per cent, and in a selected group of patients, the thyrocardiacs, it was approximately 3 per cent.

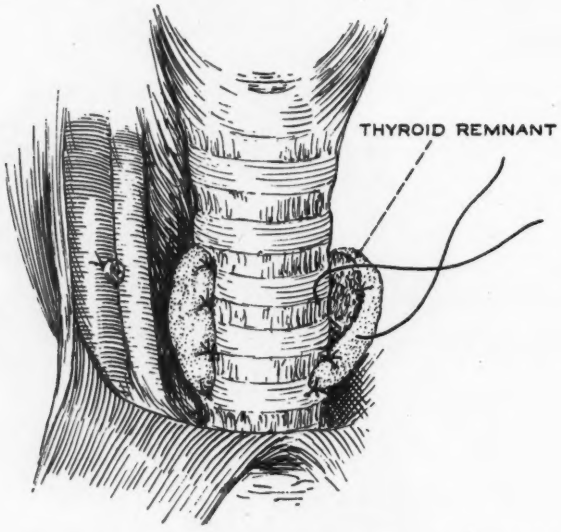

FIG. 2. A small remnant remains after radical subtotal thyroidectomy. The anterior edge of the remnants is sutured by interrupted sutures to the fascia of the trachea. (From Surgical Clinics of North America, June 1949. Published with the permission of W. B. Saunders Company, Philadelphia.)

Operative Procedure

All thyroidectomies were carried out under general anesthesia, utilizing nitrous oxide-oxygen-ether or ethylene-oxygen-ether anesthesia. The majority of patients had the anesthetic given through an endotracheal tube. Cyclopropane has not been used because of its effect on the heart, particularly as evidenced by changes in rhythm. No patients have been operated on under local anesthesia.

The technic of subtotal thyroidectomy will not be described. The operation is carried out routinely by the division of the prethyroid muscles and with a wide lateral dissection and exposure. All four thyroid arteries are ligated, the superior thyroid vessels being ligated and divided and the inferior thyroid arteries ligated in continuity (Fig. 1). Two or more parathy-

roids are routinely visualized. The recurrent laryngeal nerves are likewise routinely exposed as the most effective means of avoiding injury (Fig. 1). The major portions of both lateral lobes and all of the isthmus and pyramidal lobes are resected, leaving small segments of the lateral lobes which are folded over to the laryngeal and tracheal fascia (Fig. 2). The wounds are routinely closed without drainage. This brief account of the procedure is outlined in order to evaluate the postoperative complications.

CLINICAL DATA

In the six-year period, May 1, 1943, to May 1, 1949, 1,630 patients with hyperthyroidism have been operated on at the Lahey Clinic. This includes all patients who have been prepared with any of the antithyroid drugs before operation. An analysis of the first 1,000 of these patients will be presented.

Type of goiter

In the first 1,000 consecutive patients operated on, there were 184 patients with adenomatous goiter with secondary hyperthyroidism. This includes the discrete nodular as well as the diffuse nodular goiter with hyperthyroidism, representing 18.4 per cent of the cases. There were 816 patients with primary hyperthyroidism (Graves' disease, exophthalmic goiter), or 81.6 per cent. In this group of 1,000 patients, 135 were listed as thyrocardiacs, these patients having either well-established auricular fibrillation or cardiac decompensation.

Operative mortality

In the total group of 1,630 patients there were 4 deaths, an operative mortality of 0.24 per cent. In the first 1,000 operations only 1 operative fatality was encountered, a mortality of 0.1 per cent. Two of the 4 deaths were from cardiovascular complications. The first death occurred suddenly, without warning, on the second postoperative day, without any evidence of postoperative reaction. Postmortem examination revealed a coronary thrombosis. The second death occurred as the result of cardiac arrest in the operating room. The third and fourth deaths were due to tracheal obstruction and must be regarded as preventable. Tracheotomy was performed in both patients within a few hours of the onset of obstructive symptoms, but must be considered to have been done too late for a successful outcome.

Postoperative hemorrhage

Postoperative bleeding has always been a possible complication of thyroidectomy. Arterial hemorrhage has been effectively controlled by ligation

of all four thyroid arteries but may still occasionally be encountered in spite of this technical precaution. Most of the bleeding encountered is from the veins of the skin flap or the anterior jugular veins but at times the inferior thyroid veins may not be adequately secured. In 1,000 consecutive patients undergoing thyroidectomy it was necessary to open the incision in 27, or 2.7 per cent. It is our practice to open any wound that becomes puffy or ecchymotic, since there is always the possibility of these conditions being followed by some degree of respiratory obstruction. In any doubtful case it seems advisable to open the flap and make certain that all bleeding is controlled.

Respiratory obstruction requiring tracheotomy

Thirteen patients out of the group of 1,000 had tracheotomy performed either at the time of operation or soon afterward, usually within forty-eight hours. Any patient with signs of respiratory obstruction has immediate indirect laryngeal examination and if the airway is encroached upon by edema or there is limited motion of the vocal cords, tracheotomy is performed at once. It should be emphasized that tracheotomy should be performed in any doubtful case, since a mild degree of respiratory obstruction may rapidly become a complete obstruction with little further warning. In the 2 fatalities that occurred from this cause, the tracheotomy was performed four and six hours respectively after the first symptoms occurred, yet this proved to be too long an interval. Nurses, interns, residents and staff physicians must all be aware of this possibility and the necessity for immediate action in order to avoid the rare fatality that may result.

In this group of 13 patients in whom a tracheotomy was performed, were 3 patients who had preoperative myxedema produced by the use of the antithyroid drugs. This occurred early in our experience and it is now appreciated that respiratory obstruction is very likely to develop in any patient with myxedema under these circumstances. Each patient routinely has a metabolism test on the day that he is scheduled for operation. If the metabolism is found to be depressed below normal, the operation is cancelled, blood is taken for determination of (fasting) cholesterol, and the patient is discharged from the hospital. Iodine medication is continued but no further antithyroid drugs are given for a period of two to four weeks. In our more recent experience, after recognition of this possibility, respiratory obstruction from this cause has not occurred.

Parathyroid tetany

The incidence of postoperative parathyroid insufficiency has increased considerably since the use of the antithyroid drugs. There is no definite evidence to support the view that the antithyroid drugs affect the parathy-

roids adversely. No change has been noted in their gross appearance or on microscopic section. Most likely the higher incidence observed is related to the increased technical difficulties which have been present. Fifteen, or 1.5 per cent, of the 1,000 patients operated upon have had a persisting tetany of some degree. An equal number has had transient symptoms lasting a short period with spontaneous recovery. In a review of an earlier series of cases, the incidence of parathyroid tetany was well below 1 per cent. The present incidence of this complication indicates to us that it is essential to visualize at least two of the parathyroids when performing a subtotal thyroidectomy.

Postoperative hypothyroidism

The incidence of postoperative hypothyroidism remains the same after subtotal thyroidectomy in patients prepared with Lugol's solution and in those prepared with any of the antithyroid drugs and Lugol's solution. Forty-five patients in the 1,000 cases, or 4.5 per cent, have required the administration of desiccated thyroid for a considerable period. Some of this number have been able to discontinue their medication after a few months. Hypothyroidism is not a serious complication and cannot be considered to be an unsatisfactory result.

Recurrent hyperthyroidism

A survey has not been completed of the entire group of 1,000 patients reported in this series. From this group of patients who have been followed for two years or more, 381 patients have been observed by clinical examination and by determination of the basal metabolic rate. Nine patients have been observed to have a recurrence of hyperthyroidism—a rate of 2.4 per cent. Five of these patients have been submitted to a second operation and have had complete relief of symptoms. In four the disease has been satisfactorily controlled by iodine medication. This incidence of recurrent hyperthyroidism is approximately the same as in our earlier reports of series of patients who had been prepared with iodine. We have been led by this experience to increase the amount of the gland that is removed at thyroidectomy.

Recurrent laryngeal nerve injury

Injury to one or both recurrent nerves has always been a serious complication of thyroidectomy. This led Dr. Lahey, in 1937, to recommend routine exposure of both the recurrent laryngeal nerves during operation in all cases. Two years ago I reported before this Association our experience with approximately 10,000 thyroidectomies in which, by routine exposure of the nerves, we decreased the incidence of unilateral nerve injury by two-thirds.

In the present series of 1,000 patients, unilateral nerve injury was found in 10, or 1.0 per cent. In addition to this small number, there were other patients who had temporary immobility of the cord as observed by indirect laryngeal inspection. We do not believe this is related to exposure of the nerve but rather to edema as a result of thyroidectomy.

TABLE 1. SURGICAL TREATMENT OF HYPERTHYROIDISM. SUMMARY—1000 PATIENTS

	Per cent	
Hemorrhage	2.7	
Tracheotomy	1.3	8.5
Postoperative hypothyroidism	4.5	
Tetany	1.5	
Nerve injury	1.0	
Recurrence	2.4	5.1
Mortality	0.2	

In Table 1, I have made a summary of the complications and sequelae of thyroidectomy in 1,000 consecutive patients prepared with antithyroid drugs and iodine. If one includes the patients who have postoperative bleeding and those in whom a tracheotomy was necessary, 4 per cent of the patients have technical complications which cause difficulty during the immediate postoperative period but which do not interfere subsequently with obtaining a good result. About an equivalent number, or 4.5 per cent, require the administration of desiccated thyroid after operation, making a total of 8.5 per cent. Operative mortality and recurrent laryngeal nerve injuries are found to have a very low incidence. It is very essential that every effort be made to reduce the incidence of parathyroid insufficiency and recurrence of the hyperthyroidism, since these two groups constitute 4 per cent of unsatisfactory results.

CONCLUSIONS

Surgery is the most satisfactory method of treatment for most patients with hyperthyroidism. It should be employed, with few exceptions, in patients with nodular goiter with hyperthyroidism.

Subtotal thyroidectomy can be carried out with a low operative mortality which has been further lowered to 0.2 per cent by the utilization of the antithyroid drugs in the preparation of patients for operation.

When antithyroid drugs are used in the preparation of patients for surgery, larger portions of the thyroid gland should be removed than after preparation with iodine.

Following subtotal thyroidectomy satisfactory results are obtained in 95 per cent of patients.

INCIDENCE OF CARCINOMA OF THE THYROID IN NODULAR GOITER*

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FOUR years ago we reviewed the data in the Illinois Research Hospital on carcinoma of the thyroid with particular reference to its incidence in goiter. We noted that carcinoma was found in 17.1 per cent of all our patients having thyroidectomy for nontoxic nodular goiter (1). One of the reasons why this figure appeared high was because other authors had failed to break down the types of goiter and had reported the incidence in all types of goiter, or in both types of nodular goiter combined. Our incidence of carcinoma in toxic and nontoxic nodular goiter was 7.2 per cent in the 1936–1944 series.

Since this figure appeared quite high, we decided a few months ago to review our recent data. By a strange coincidence, the incidence of carcinoma in nontoxic nodular goiter was found to be almost identical, namely, 17.2 per cent.

The incidence of carcinoma in toxic nodular goiter varies considerably as would be expected, largely because there is considerable difficulty in determining whether or not certain mild symptoms should be interpreted as being produced by thyrotoxicosis. In 378 toxic nodular goiters we found carcinoma present in only 4, constituting an incidence of 1 per cent (Table 1). Our incidence of carcinoma in 517 cases of toxic diffuse goiter was 0.2 per cent. All authors have noted a very low incidence in this type of goiter. For example, Ward (2) has reported only one case of carcinoma in 1,900 cases of toxic diffuse goiter, although a year ago Pemberton and Black (3) reported an incidence of 0.4 per cent in 3,500 cases.

The incidence of carcinoma in solitary nodules is much higher than in multinodular goiter; for example, in our first series reported in 1944, we noted an incidence of carcinoma of 24 and 11 per cent respectively in the two groups. Since other authors have broken down their series into comparable groups, the same high incidence of carcinoma in solitary nontoxic nodular goiter has been noted. For example, Crile has noted an incidence

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TABLE 1. INCIDENCE OF CARCINOMA IN NODULAR GOITER (INCLUDING TOXIC, NONTOXIC, AND CARCINOMA) AT THE ILLINOIS RESEARCH HOSPITAL, 1936–1948.

Type of goiter	1936–1944		1944–1948		1936–1948	
	No. of cases	Per cent carcinoma	No. of cases	Per cent carcinoma	No. of cases	Per cent carcinoma
Toxic nodular	330	1.2	48	0	378	1.0
Solitary	(71)	0.0	(17)	0	(88)	0.0
Multinodular	(259)	1.6	(31)	0	(290)	1.4
Nontoxic nodular	192	17.1	93	17.2	285	17.15
Solitary	(92)	24.0	(51)	(25.5)	(143)	(24.4)
Multinodular	(100)	(11.0)	(42)	(7.1)	(142)	(9.8)
Total	522	7.2	141	11.3	663	8.0

TABLE 2. INCIDENCE OF CARCINOMA IN NODULAR GOITER AS OBTAINED FROM NUMEROUS REPORTS IN THE LITERATURE

Author	Number of patients with nodular goiter (toxic and nontoxic)	Per cent carcinoma in nodular goiter (toxic and nontoxic)	Number of patients with nodular nontoxic goiter	Per cent carcinoma in nodular nontoxic goiter	Per cent carcinoma in solitary nontoxic nodular goiter
Brenzier & McKnight (6) Charlotte, N. C. 1940	2,324	4			
Horn & assoc. (7) Philadelphia, Pa. 1947	1,135	6.3	637	9.8	
Crile Cleveland, Ohio 1948	537	5.6	274	10.9	24.5
Ward San Francisco, Calif. 1947	3,539	4.8			15.6
Cole & assoc. Chicago, Ill. 1948	663	8.0	285	17.1	24.4

of 24.5 per cent carcinoma in solitary goiter, although Ward records an incidence of only 15.6 per cent (Table 2).

Although it has long been known that goiter is a geographic disease, that fact seems to be forgotten, particularly when the incidence of carcinoma is being considered. There is ample statistical evidence to prove the point regarding incidence of goiter. For example, Rogers and associates (4) recently noted that in 544,918 patients admitted to the Boston City Hospital, the Massachusetts General Hospital and to Johns Hopkins Hospital over a period of several years, only 0.59 per cent were admitted to the hospital because of a goiter. We made a survey of 68,573 admissions to the Illinois Research Hospital over a period of eleven years and found that 1.7 per cent of the patients coming to the hospital came because of a goiter. This incidence of goiter in our patients is almost exactly three times greater than the incidence in the patients reported in the series by Rogers and associates.

We should also like to comment on the failure of autopsy figures to reflect correctly the incidence of carcinoma of the thyroid. For example, over a period of the last four years our Department of Pathology has had only 2 autopsies for carcinoma of the thyroid. However, during this same period we know that 11 of our patients with carcinoma of the thyroid have died. None of these 11 was autopsied in our hospital. The 2 who were observed came from our previous series. We did not refer any of our patients with inoperable carcinoma of the thyroid to the hospital in the moribund state for autopsy, largely because beds are so scarce that there is not room even for patients with acute conditions. Since we already knew the diagnosis in our patients with metastases, and knew there was nothing more we could do for them, we did not refer them to the hospital. Most of them died at home, although we assume that perhaps a few might have died in other hospitals.

It might be said that our high incidence of carcinoma in toxic nodular goiter is related to too much liberality in making the diagnosis. Unfortunately, our follow-up for our first series for 1936–1944 was poor. However, when we had evidence that carcinoma of the thyroid appeared to be present in such great frequency, we decided to follow all subsequent patients very carefully. We are now able to report a 100 per cent follow-up in patients with carcinoma of the thyroid since 1944 to date. Of 16 patients with carcinoma of the thyroid observed between 1944 and a few months ago, we know that 11 are already dead. About half of these were inoperable when we first saw them. A twelfth patient has metastasis; a short time ago we resected the sternoclavicular joint for a metastasis which decreased in size under radioactive iodine, but did not disappear. We assume that this patient has other evidence of metastasis, but knowing that the survival time in carcinoma of the thyroid is extremely variable, it is possible that

this patient might live for several years. In our study we noted that the danger of malignancy in a nodule in the gland of a male patient is about three times as great as in females. This increased danger in males over females has already been called to our attention by Ward (2).

It is also well known that carcinoma of the thyroid is a disease of relatively young people. The average age in 54 patients observed in our hospital between 1936 and 1948 was 48 years. This is slightly greater than the age of patients with toxic nodular and nontoxic nodular goiter, which was 43.5 and 42.4 years respectively. The incidence of carcinoma in children as reported by Kennedy (5) emphasizes the danger in youth. For example, in 62 children under the age of 14, Kennedy noted the incidence of carcinoma was 19.3 per cent. Ward (2) reported an incidence of 40 per cent in 10 children under the age of 14 with nontoxic nodular goiter.

There is much discussion relative to the site of origin of carcinoma, but that point does not come within the scope of our presentation today. However, we believe it would be of interest to report our figures on the duration of the mass in patients with benign versus malignant goiter. For example, in 54 patients with carcinoma of the thyroid the duration of the mass was 6.1 years. In 378 patients with toxic nodular goiter, and 285 patients with nontoxic nodular goiter the duration was 9.9 and 10.2 years respectively. The six-year duration of the nodule in our patients with carcinoma of the thyroid would suggest that in most patients a pre-existing nontoxic nodular goiter was present for a few years, particularly since most of the patients give a history of rather sudden growth a year or two before they come into the hospital. However, we must admit that the growth of carcinoma of the thyroid is an extremely variable factor, and that a carcinoma might exist for some time without revealing significant growth.

In his discussion here today, and elsewhere, Dr. Crile has brought up two very important points regarding the incidence of carcinoma in nodular goiter. He has emphasized that a certain amount of screening has already taken place before we see patients with nodules of the thyroid. To a great extent the patient himself takes part in this screening, particularly since he delays for a considerable time before seeking advice, and has been told that as long as no sudden increase in growth occurs he need not go to a physician. The internist likewise acts in this screening process, insofar as he frequently refers only suspicious cases to the surgeon. We agree that a certain amount of screening has taken place before the patient arrives in the surgeon's office, or in the admitting clinic of a charity hospital. In reality, we should speak of the incidence of carcinoma in the hospital as related specifically to that type of patient. In other words, the incidence of carcinoma in patients having thyroidectomy is by no means the incidence of malignancy in patients with goiter who have not yet gone to a physician

for care relative to the goiter. However, we should add that our incidence of carcinoma in nontoxic nodular goiter has not decreased in our second series (1944–1948), even though during this period we have advised thyroidectomy in all patients in whom a nodular nontoxic goiter has been discovered. With very few exceptions, our patients heed our advice and submit to thyroidectomy.

SUMMARY

Since the incidence of carcinoma in nontoxic nodular goiter as reported by us in 1944 appeared so high (17.1 per cent), we made a similar study of our records during the next four years and discovered an incidence almost identical (17.2 per cent). One of the reasons our figures on incidence of carcinoma in nontoxic nodular goiter appeared so high was because we were the first authors to break down the goiters into the 3 different types, showing the incidence in each group. For example, our incidence of carcinoma in patients having thyroidectomy for all 3 types of goiter (nontoxic nodular, toxic nodular and toxic diffuse) was only 4.6 per cent.

For decades, and even centuries, the medical profession has known that goiter is a geographic disease. It appears plausible that carcinoma of the thyroid could likewise be geographic. At least, it appears that there might be a geographic relationship in regard to the invasive character of the disease, particularly since of 16 patients we have observed in our clinic with carcinoma during the past four years, 11 are already dead and a twelfth patient is known to have metastases. Thus, 70 per cent of patients with carcinoma of the thyroid in our second series are already dead, even though the maximum observation time in the series was only four years.

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WHAT THYROID NODULES ARE TO BE FEARED?*†

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IN 1947 two articles appeared from the Eastern Seaboard of the United States minimizing the importance of carcinoma of the thyroid (1) (2). In the first, this disease was described as a rare cause of death. This assumption was based on the low incidence of carcinoma of the thyroid found at autopsy at three hospitals in Boston. The author was unable to explain why the incidence found by him was so low in contrast to reports of others and suggested that the pathologic criteria used in making the diagnosis were responsible.

The second article reported a study of both clinical and autopsy material at three hospitals. The incidence of carcinoma of the thyroid in the periods studied was found to be less than that reported elsewhere, and virtually no greater than the mortality rate of prophylactic surgery in nodular goiter at two of the hospitals. Since there was an undesirable complication rate in addition, strong doubt was expressed regarding the advisability of such prophylactic surgery.

These reports are at variance with the experience of others. Cancer of the thyroid exists along the Eastern Seaboard as well as in the goitrous districts of the United States. Since both of the above papers were based upon statistics gathered in part from the Massachusetts General Hospital, and since the experience and considered opinion of the Thyroid Clinic of this hospital differs from the conclusions reached in both papers, it seems proper to set before you the reasons leading to our opinion and the policy of management of carcinoma of the thyroid at the Massachusetts General Hospital.

Incidence of carcinoma of thyroid at the Massachusetts General Hospital

The incidence of carcinoma of the thyroid at the M.G.H. has been determined over the twelve-year period from January 1937 through Decem-

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ber 1948. It is divided into that in the hyperplastic goiter of Graves' disease, that in all nodular goiters, and that in goiters consisting of a single nodule. The findings are a reproduction of those in reports from other clinics spread over the American continent.

A lesion was considered to be malignant only if there was local invasion of the capsule and neighboring tissue or if it had spread to lymphatic nodes,

TABLE 1. CARCINOMAS ENCOUNTERED 1937–1948

Type	No.	Av. age of patient	Age range
Papillary	62	46	16–76
Alveolar	24	48	17–62
Undifferentiated	27	58	32–80
Epidermoid	2	62	56–67
Lymphoma	1	65	
Retic. cell sarcoma	2	65	55–76
Metastatic	12	56	39–74
Total	130		

TABLE 2. ORIGIN OF CARCINOMAS METASTATIC TO THE THYROID

Rectum	2
Thyroglossal duct	2
Lung	1
Esophagus	2
Kidney	2
Larynx	3
Total	12

bone or other organs. Papillary cystadenomas without such invasion were classified as benign. Blood vessel invasion was not accepted as a sufficient criterion for malignancy. The benign metastasizing type of goiter was considered malignant only when a distant metastasis was demonstrable.

In the twelve-year period, 6 incidental cancers were found in the diffusely hyperplastic goiters of patients with hyperthyroidism, an incidence of less than 1 per cent (0.8 per cent). Five of the carcinomas were of the papillary type and 1 of the alveolar type.

The incidence of malignancy in nodular goiter is significantly higher than in hyperplastic. Of 1,109 nodular goiters operated upon, there were 112 which harbored a malignant lesion of a tissue of the thyroid gland, an incidence of 10.1 per cent. In an additional 12 nodular goiters, the cause of

one or more nodules was found to be a metastasis from a malignant tumor arising elsewhere than in the thyroid gland. The distribution of the type of all carcinomas found both in hyperplastic and nodular goiter is given in Table 1. The organ of origin of the metastatic tumors is given in Table 2.

Because of the impression long held at this Thyroid Clinic (3) and elsewhere (4), a special study was made of the incidence of malignancy in goiters consisting either of a single nodule or in which the only demonstrable abnormality was localized to one area of the thyroid.[1] Starting in early 1944 every patient was operated upon who by physical examination was judged to have either a single nodule or a goitrous mass localized to one thyroid lobe. In either case the criterion of localized disease was satisfied if the remainder of the thyroid was felt to be normal. No selection was permitted, patients believed to have a benign lesion, such as a cyst, being included. In the first 76 patients the lesion proved to be malignant in 17, an incidence of 22 per cent. When the series had reached 156, there were 29 malignant lesions, the incidence being 19 per cent.

Because it is possible to be more accurate in the clinical diagnosis by applying criteria other than mere localization, the consecutive series has not been carried any further. It is our belief, however, that this small series of unselected cases proves the incidence of cancer to be higher in goiters in which the disease is localized to one area than in nodular goiter with diffusely distributed nodules.

It does not necessarily follow that the incidence of carcinoma of the thyroid found at the M.G.H. is the true incidence of the disease in the community or in New England. Inevitably there is some selection in the cases being sent to or filtering through to such a hospital. We believe prehospital selection is particularly likely to have taken place in the single-nodule series because it was started simultaneously with the study of the functional activity of nodules by means of radioactive iodine. Nearly all of the patients of this single-nodule series received tracer doses of radioactive iodine immediately before operation, and the uptake of radioactive iodine was measured in the resected tissue. A number of doctors outside the hospital staff knew of this isotope study. In referring patients to us, the doctors having our tumor study in mind may have inadvertently selected those patients with goiters which they were particularly suspicious of being malignant.

Whether the incidence of carcinoma of the thyroid at the M.G.H. is the exact statistical incidence for New England is not the point at issue. What is important is that the disease is to be contended with and must be kept in mind. It is rarely found in the hyperplastic goiter of Graves' disease, is

[1] This study was initiated in collaboration with Dr. Rulon W. Rawson before he moved to the Memorial Hospital in New York.

more commonly found in nodular goiter, and is most commonly found in patients with a goiter in which abnormality is localized to one area of the gland. Such statistics should not occasion surprise when it is recalled that by definition neoplasia is a localized cellular change.[2]

The author of the first article minimizing the importance of carcinoma of the thyroid judged its incidence and significance by hospital autopsy statistics. Review of our hospital's total experience with the disease shows how fallacious reasoning may be which is based upon such limited statistics; he reported our autopsy incidence to be less than 1:1,000 in 11,000 autopsies. Certainly that is a low incidence but since the great majority of the patients with thyroid cancer treated at this hospital die outside the hospital and without autopsy, the statistics have no bearing upon the true incidence or importance of the disease in the community.

Unfortunately the conclusions of this first article have received undue credence. A case report serves to substantiate this statement.

In June 1948 a middle aged woman was referred to our Thyroid Clinic because of a goiter producing severe pressure symptoms. Ten months previously she had been referred to a medical clinic, the physicians of which were imbued with the concept that cancer of the thyroid was so rare it scarcely existed as a clinical entity, a concept based to no inconsiderable extent on the above mentioned first article. At that clinic the functional activity of her thyroid gland had been thoroughly and repeatedly studied. At one visit she had been seen in consultation by a surgeon who had advised excision of what he described as a thyroid adenoma. The reply of a senior physician to this consultation was that such surgery was unnecessary.

The goiter continued to enlarge; it spread from one lobe of the thyroid to that on the other side and pressure symptoms appeared. Alarmed, she sought other advice. By the time the patient had reached us, an obvious carcinoma had invaded pharynx and esophagus to an extent which made complete extirpation impossible. Incomplete excision followed by heavy external irradiation failed to check the course of the disease and she died (outside the hospital and without autopsy!) six months later from strangulation.

[2] *Definition of neoplasia*: A neoplasm is an area of tissue growing without regard to the normal needs of cell regeneration and out of bounds of normal physiologic control. No neoplasm is known which afflicts an entire organ or tissue from its inception. A neoplasm starts in one area only—never spontaneously and evenly throughout the whole. Thus from the anatomic point of view a neoplasm is in contrast to hyperplasia or hypertrophy, growths affecting the whole simultaneously and to comparable degree.

Neoplasms may be either benign or malignant. The distinction between benign and malignant is drawn anatomically by the following criteria—benign displaces but does not invade the neighboring tissue; the benign does not metastasize.

The malignant neoplasm may be further defined by functional characteristics. The growth of the malignant neoplasm is unbridled and the rate of growth exceeds that of the benign. The cells of the malignant neoplasm have a less than normal functional capacity.

Cancer of the thyroid gland is no exception to this definition. Only in those cancers of the rapidly infiltrating, round cell type and of long enough standing for the entire thyroid gland to have been invaded, does the thyroid gland appear to be evenly involved.

Our considered opinion takes issue with the authors of the second article minimizing the importance of carcinoma of the thyroid on two points and agrees with them on another. They arrive at a lower figure for the incidence of carcinoma at our hospital than we do. This is apparently due to two causes. First, their sampling of our experience covered a shorter period than our own; and second, they diluted their figure for the incidence by calculating it on the basis of all types of goiter operated upon, including thyrotoxic hyperplasia. Had they stopped to consider the differences in the nature and life history between malignant neoplasia and diffuse hyperplasia with thyrotoxicosis, they would not have made this dilution.

We agree with their hesitation over prophylactic surgery for nodular goiter, not because of the surgical complications which they report but because we question the rationale when it is applied to diffusely disseminated nodular goiter. If a nodule of the thyroid is a precursor of cancer and there is but a single nodule in an otherwise normal thyroid gland, excision of this nodule as a prophylactic measure against the future development of cancer makes sense. If, on the other hand, all of the thyroid tissue is abnormal as is the rule in the majority of nodular goiters, then the only rational operation from the prophylactic point of view is bilateral, total excision of the thyroid tissue. It is common practice, however, in such goiters to do only a partial or subtotal resection. To be sure, with some of the diseased thyroid tissue removed there is less diseased tissue left for cancer to develop in. On theoretical grounds, however, it can be suggested that there is a greater likelihood of cancer developing in the remnants per gram of tissue than in the whole goiter. If it is agreed that the hyperplastic process may have something to do with the genesis of malignant neoplasia, then the small remnants following subtotal resection should have a greater likelihood of undergoing malignant degeneration because the hyperplastic stimulation of the remnant is intensified by subtotal resection. Indeed it seems that the enthusiasts for prophylactic surgery in nodular goiter are open to the criticism that they have not considered adequately the physiologic aspect of the pathogenesis of nodular goiter. A case report again serves to substantiate this statement.

A woman, in her late fifties when first seen by us in April, 1947, had been operated upon in 1935 at another hospital. A "multiple colloid adenomatous thyroid, non-malignant" had been subtotally resected. The goiter recurred and in 1938 she was seen in consultation by a second surgeon. The basal metabolic rate was minus 14 per cent. A second subtotal resection was performed by the two surgeons in collaboration.

In 1941 the basal metabolic rate was minus 19 per cent and the administration of desiccated thyroid was started. In 1945 the thyroid medication was stopped.

At the end of 1946, a second regrowth of the goiter was noticed. During the four months prior to our seeing her, the regrowth increased appreciably and her family physician referred her to a third surgeon, the surgeon in charge of the tumor clinic of a

large general hospital. Immediate reoperation was advised and with a warning as to the probable nature of the goiter.

The family physician and the patient were dissatisfied with this advice, both wondering why a third operation should succeed when the first two had failed. Our opinion was therefore sought.

Examination revealed an irregular, firm, fixed mass occupying the region of the right side of the thyroid isthmus and adjacent area of the right thyroid lobe. There were no palpable lymph nodes. Puffiness of the eyes was absent but the pulse rate was 60.

The texture and shape of the goiter were consistent with carcinoma but were also explicable on the basis of a regenerating colloid goiter, scarred by the fibrous tissue legacy of two operations. The impetus for the regeneration theoretically could have emanated from the continued subnormal thyroid hormone output, judged to be present because of the low metabolic rate.

The latter diagnosis being the more reasonable, the patient was started on desiccated thyroid, 65 mg. daily. Within one month, she recognized the disappearance of a sense of constriction in the throat, a symptom which had heretofore passed unnoticed. Examination revealed that the goiter had become softer and decreased in size. The basal metabolic rate was minus 6 per cent and the pulse rate 70. The patient has taken thyroid since that time, the dose having been doubled sixteen months later. The goiter has become reduced in size to a soft remnant, only 30 per cent of the initial size. The patient feels generally better than she has for years and an old irregularity of her toenails has disappeared.

What this patient's goiter needed was a little help, a boost, a release from the urging to produce more hormone. "Prophylactic surgery" would only have increased the hypothyroidism and the urging.

Policy of management

The policy governing the management of patients with nodules of the thyroid at the Thyroid Clinic of this hospital is based more upon the definition of neoplasia than upon the statistical instances of malignant degeneration in the various types of goiter. This statistical incidence is but an expression of the probability of such degeneration. It is useful, therefore, in deciding what to do with a goiter once an anatomic diagnosis is established. When faced with a patient who has a goiter, the nature of which is not established, the statistical probability must be used with caution in reaching a diagnosis. Decision regarding diagnosis and what to do with the patient at that moment rests upon the clinical and laboratory findings in that individual patient.[3]

Recognition of neoplasia in the thyroid gland on physical examination depends primarily upon identification of a process present in one area and absent elsewhere in the gland. This is in keeping with the definition of

[3] It is unfortunate that the history of a goiter given by the patient is so seldom definitive in reaching a decision in regard to the differential diagnosis. It is only when the history is punctuated by the accurate physical findings of a qualified observer that it is of tangible or direct aid.

neoplasia as a localized disease. Such recognition is relatively easy when the disease is in the form of a single nodule and the remainder of the gland is normal. It is less easy when the whole of the gland is nodular and recognition of neoplasia depends upon differentiating the character of one nodular area apart from the whole. The local characteristics of hardness, irregularity and adherence are helpful adjuncts in indicating malignancy but may be misleading owing to the presence of inflammation.

The hope of adequate therapy is increased the earlier the lesion is recognized. Although spread of the carcinoma into the neighboring tissue and lymphatics generally indicates a primary lesion of considerable duration, some thyroid cancers, particularly the papillary type, may metastasize early into the lymphatic channels. Search for lymph node enlargement, an indication of metastasis, is always indicated even when the suspected primary lesion is still small and not locally invasive.

It is not within the scope of this paper to give in detail an account of the spread of carcinoma of the thyroid into the lymphatic channels. I should like to point out, however, a lymph node or group of lymph nodes, the Delphian node, which has not received attention elsewhere but which we have found of great usefulness in identifying the early spread of cancer of the thyroid into the lymph nodes (5).

The Delphian node, named after the oracle of Delphi, lies in the midline of the neck just above the upper border of the thyroid isthmus and in front of the middle cricothyroid ligament. Anterior to it lies the first cervical fascia and the skin. Normally the lymph node is not palpable but if it is enlarged and firm from invasion of metastatic carcinoma, it is readily palpable for two reasons. First, there is no platysma overlying it because the platysma muscle does not come to the midline, there being a gap between the muscles on the two sides. Second, it can be felt against the firm cricoid cartilage or cricothyroid ligament beneath it and can be rolled under the fingers. There is difficulty in feeling lymph nodes elsewhere in the neck during the early phase of their enlargement from metastatic cancer because they are easily displaced or depressed against the soft tisssues around and behind them. It is not until enlargement is more advanced that they can be felt against the jugular vein, for example.

The location of the Delphian lymph node is shown in Figure 1. The lymph node is almost always normally present. At 152 operations at which this lymph node was specifically looked for it was found in all except nine cases, or 94 per cent. In 64 per cent of the 152 cases but one lymph node was found. In 21 per cent two nodes were found: in 6 per cent, three nodes; and in 3 per cent, four or five nodes. When the nodes are multiple they are clustered together. The higher number of nodes was found generally when disease was present in the thyroid associated with lymph node enlargement, that is, carcinoma, thyroiditis or Graves' disease hyperplasia.

In the last 13 cases of cancer upon which I have personally operated, and which had not had a previous operation elsewhere, the Delphian lymph node was found to have been invaded in 9. In 5 of these the Delphian node had been palpable preoperatively and a diagnosis of cancer with invasion of the lymphatic system made because of this finding. In the other 4 in which there was positive invasion, the lymph node enlargement had

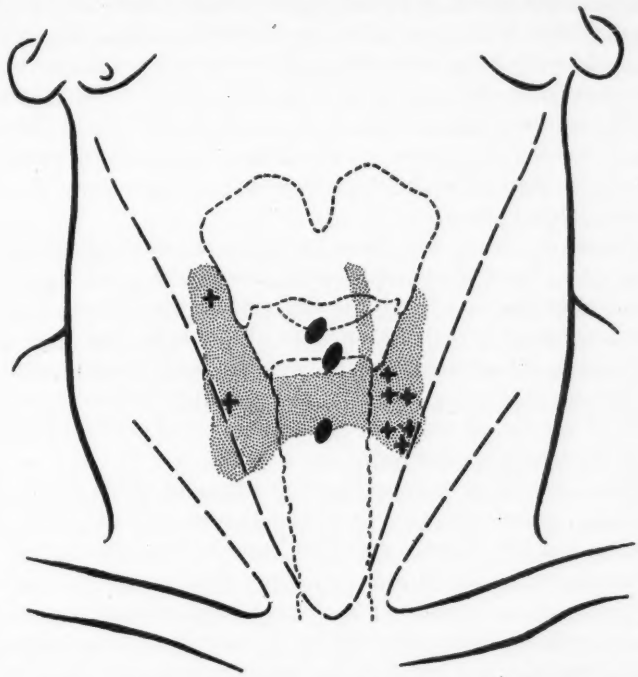

FIG. 1. Anatomic relation of the Delphian lymph node to the thyroid gland and larynx. The two black oval bodies above the thyroid isthmus medial to the pyramidal lobe and in front of the cricoid cartilage represent a double Delphian node group. The less constant, pre-isthmic node is depicted by the third black oval body overlying the lower border of the thyroid isthmus. The crosses on the lateral thyroid lobes indicate the position of thyroid cancers found to have metastasized to the Delphian node.

not reached sufficient size for the node to be palpable preoperatively. In the 4 cases in which there was no microscopic evidence of invasion of the Delphian node, even though cancer was present in the thyroid gland, the lymph nodes were normal in size.

The Delphian lymph node is useful not only as a preoperative sign of carcinoma with early lymphatic invasion but also as a means, early in the operative exploration of the thyroid gland, of making a diagnosis of carcinoma. It is now established policy in operating on the thyroid and para-

thyroid glands to look at the Delphian node group as the first step after raising the upper and lower skin and platysmal flaps. As the sternohyoid muscles are separated in the midline, the Delphian node is readily accessible immediately above the thyroid isthmus. It is found just beneath the most anterior sheath of the second cervical fascia as it folds over the upper border of the thyroid isthmus. If a pyramidal lobe of the thyroid is present, the lymph node group will be found in the midline immediately medial to the pyramidal lobe. If the lymph node is enlarged or firm, it is excised and sectioned at the table for gross evidence of metastatic invasion. It has been possible to recognize early invasion with only a part of the lymph node involved. If necessary, frozen section is taken of one half of the node. If carcinoma is found to be present in the lymph node, radical operation for thyroid cancer is planned without the necessity of cutting into the primary lesion in the thyroid gland.

The Delphian node has also been found enlarged in thyroiditis of the Hashimoto type, hyperplasia of Graves' disease, amyloid disease of the thyroid and infection of a low-lying thyroglossal duct cyst. The last enlargement associated with infection was obvious. In the hyperplasia of hyperthyroidism, the enlargement has seldom been great enough for the nodes to be palpable preoperatively. At operation, however, a moderate hyperplasia of the lymph nodes of this group and of others in the thyroid region was commonly recognized.

Thyroiditis represents the principal problem of differential diagnosis with carcinoma when enlargement of the Delphian lymph node group is found. In the last 10 patients operated upon by me who proved to have chronic thyroiditis of the Hashimoto type, the lymph nodes have been clearly hyperplastic in 8 cases. In 5 of these 8 the enlarged lymph node or nodes were palpable before operation. In only 2 of these was one node found; the remainder had from two to four enlarged nodes. In only 1 of the 10 cases was the lymph node within normal limits of size and consistency and the tenth case was one of those rare ones in which no Delphian node was found. In 1 case of amyloid invasion of the thyroid an enlarged Delphian node was felt preoperatively and its presence substantiated at operation. It too was invaded with amyloid.

There is a second lymph node which, when enlarged, is readily palpable. This node lies in the midline between the sternohyoid muscles in front of the lower border of the thyroid isthmus and because of its position is being called the pre-isthmic node. It has been felt as an enlarged node preoperatively in 1 case of cancer and 1 of thyroiditis. It has by no means the same constancy as the Delphian node; I have only been able to find it 5 times at routine search. In one of these cases no Delphian node was found.

Because of its constancy of occurrence, palpable position and frequency

with which it is invaded by cancer of the thyroid when spreading into the lymphatics, the Delphian node appears to be a valuable diagnostic adjunct both before operation and at operation. Careful search for this lymph node should be made as a part of the routine physical examination of every thyroid gland.

Deviation from normal of functional activity within various areas of the thyroid gland is a laboratory measurement which may prove useful in the preoperative diagnosis of carcinoma of the thyroid. In the functional part of the definition of malignant neoplasia it is to be recalled that malignant cells are relatively undifferentiated and in general are believed to have a less than normal functional capacity. Dobyns (6) has made an extensive survey, using radioactive iodine, of the functional activity of various types of thyroid lumps. These studies are still in the formative stage but there is sufficient evidence available to show that, if on scanning a nodular goiter twenty-four to forty-eight hours after a tracer dose of radioactive iodine, a lump is found to have emanating from it a greater concentration of radiation than from the adjacent thyroid tissue, this lump is a hypersecreting piece of tissue and not malignant. (The single exception to this which has been disclosed is the adenoma with differentiated cells, the so-called benign metastasizing goiter, 2 of which with metastases to bone have been studied.)

If from a thyroid lump, on the other hand, the emanation is weaker than from the surrounding thyroid tissue, it must be realized that malignancy may be present. In many of the colloid nodules of nodular goiter less than normal secretory activity is found, as judged by radioactive iodine uptake (7). Also in many benign adenomas of the thyroid there is less than normal activity. In all of the cancers of the thyroid, with the exception of the 2 benign metastasizing goiters, the uptake of radioactive iodine has been significantly less than that of the normal, uninvaded thyroid tissue. Use of this laboratory test as an adjunct to the physical diagnosis makes more certain the clinical diagnosis of cancer.

COMMENT

In spite of accurate physical and laboratory examinations, a satisfactory diagnosis cannot be made in many a thyroid lump without surgical exposure and occasionally surgical biopsy. Until more is understood of the pathologic biology of tumor cells, it is likely that we shall have to content ourselves with the type of measurement now made. Further refinement, both clinically and in the laboratory, by use of such signs as the Delphian node, is still possible. When clinical measures fail, it must be emphasized that operation is often indicated for no other reason than to make a diagnosis. In such cases, it is the surgeon's duty to take all measures to estab-

lish this diagnosis before undertaking excision. Only when the diagnosis is established can the appropriate en bloc surgical excision be planned.

SUMMARY

The incidence of carcinoma of the thyroid for the twelve-year period from 1937 through 1948 at the Massachusetts General Hospital has been less than 1 per cent in hyperplasia of Graves' disease, 10 per cent in all nodular goiters, and 19 per cent in goiters consisting of single nodules or localized abnormalities. One hundred and twenty-nine cases of cancer originating in or invading the thyroid gland have been encountered. This incidence and the types of cancer found substantiate the reports from other parts of this country and do not lend credence to recent reports from the Atlantic Seaboard suggesting that cancer of the thyroid is of little clinical significance.

The localized nature of cancer in contrast to the diffuse involvement of hyperplasia or hypertrophy is pointed out. The use of the principle of localization in making a diagnosis is stressed.

Attention is called to the Delphian lymph node as an early sign of the spread of thyroid cancer into the lymphatics. Thyroiditis of the Hashimoto type is also commonly associated with enlargement of this lymph node group.

The study of the functional capacity of malignant thyroid tumors indicates that malignant tumors have less than normal functional capacity. The use of this principle in scanning the goiter of a patient following a tracer dose of radioactive iodine is described.

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THE NATURAL HISTORY OF THYROID CANCER

A REVIEW OF 301 CASES*

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THE natural history of cancer of the thyroid is not a subject that lends itself to easy exposition, since to develop it properly one would have to have at his disposal a large number of cases of thyroid cancer that were entirely untreated. We have no such body of material and know of no published account of substantial numbers of untreated thyroid cancers. Hence, this discussion will of necessity deal chiefly with the natural history of the disease up to the time that it was proved to be thyroid cancer. It will be seen that after treatment the natural history of some forms of thyroid cancer is substantially altered, whereas in others it is little affected.

All students of thyroid cancer recognize that there are wide differences in the clinical behavior in the major histologic types of these tumors. It is less well known, however, that considerable variations in the clinical course of tumors falling within the same broad histologic grouping, may well be expected.

MATERIAL

This report is based on 301 cases of thyroid cancer, studied at the Memorial Hospital during the years 1930–1946 inclusive. Since only 215 of these patients have been followed for the customary five-year period, cure rates will not be stressed in this report. It might be said, however, that we believe the five-year yardstick as a criterion of cure in some forms of thyroid cancer to be of limited value. The study of the natural history of this disease makes one feel that one should be exceedingly cautious about using the term "cure" in connection with certain forms of thyroid cancer.

The material here presented cannot be considered comparable to any other series with which we are acquainted. One hundred and fifteen or 38.6 per cent of the 301 patients in this series had prior efforts at definitive treatment before coming to our clinic. By definitive treatment we mean treatment which, by ordinary standards, had been designed to arrest or

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cure the disease. Such treatments include subtotal thyroidectomy, with or without postoperative irradiation, thyroidectomy plus neck dissection, biopsy plus irradiation, or irradiation only. Previous methods of treatment had obviously failed, since almost all of these patients had evidence of residual, recurrent, or metastatic disease on admission to our clinic and a significant number were little short of being moribund. The fact that almost 40 per cent of the patients in this series had been operated upon or irradiated elsewhere for from six days to twenty years previously, makes their clinical course of considerable value in tracing the natural history of the disease under certain conditions of treatment. Naturally, we see few successful results of other surgeons but the volume of unsuccessfully treated patients coming to our clinic indicates that we are seeing a fair percentage of the failures of treatment in our community. Since so large a percentage of these patients represent treatment failures, it makes one doubt the efficacy of the methods used. For this reason, in recent years we have adopted a more radical approach to the treatment of thyroid cancer of all types.

The histologic material from these cases has been reviewed and a simplified histologic grouping devised. Although the classification is not considered ideal, it is based on a correlation of histologic structure with clinical course.

TABLE 1. THREE HUNDRED AND ONE CANCERS OF THE THYROID AT MEMORIAL HOSPITAL DURING THE PERIOD 1930–1946*

	No. of cases	Per cent
1. Papillary adenocarcinoma	139	46
2. Follicular and alveolar adenocarcinoma	22	7
3. Solid adenocarcinoma	56	19
4. Giant cell carcinoma	39	13
5. Hürthle cell carcinoma	27	9
6. Unclassified†	18	6
Total	301	100

* Lymphosarcomas and squamous carcinomas omitted from this discussion.
† Histologic material not adequate to classify.

Papillary adenocarcinomas

These tumors made up the largest histologic group in the series. This is fortunate, since they are the least malignant of all thyroid cancers. The youngest patient with this type of tumor was 6 years old and the oldest was 78. These tumors were most frequent during the fourth and fifth

decades, the median age being 43 years. This is the characteristic thyroid cancer of youth and childhood. Of the 25 patients in the entire series who were 21 years of age or younger, 20 had tumors which were papillary. Sixty-five per cent of the patients were females and 35 per cent were males. Seventy-four per cent of the 139 patients with papillary tumors had been aware of a pre-existing goiter. In the other 36 patients the primary tumor was discovered after the development of metastasis. Data gathered on the probable duration of the goiter proved exceedingly unreliable. In like manner, the date of onset of the cancer developing on the basis of a pre-existing goiter, was intriguing but problematical. Thirty-six per cent of these patients had known of their goiters for less than one year, whereas 21 per cent of the patients in this group had been aware of thyroid enlargement for periods varying from six to twenty years or longer. Actually the duration of any thyroid cancer is exceedingly difficult to determine. Our material contains limited anatomic evidence illustrating the role of benign goiters in the development of thyroid cancer. It is very likely that this is a quality of thyroid cancers that develop in areas where goiters are not endemic. Our findings in no wise are a contradiction to established viewpoints on this topic.

Findings on admission: Papillary tumors are often distinguished by extremely small rather than large size. Fifteen per cent were less than 1 centimeter in diameter. The general range in size was from 2 to 4 centimeters, but on occasion they may assume large dimensions. Eighty or 58 per cent of the patients showed cervical nodes on admission and these nodes were bilaterally involved in 18 patients or 13 per cent of the cases. In some instances the bulk of the metastatic disease in nodes may completely overshadow a minute primary in the thyroid. Other findings on admission include laryngeal, tracheal, and esophageal obstruction which are signs of advanced disease. Nine of these patients had chest metastasis on admission and in 4 there were osseous lesions. Bizarre findings include metastasis to an eye in one patient and a thyroid mass presenting within the larynx in another.

Clinical course: Papillary tumors often have an extremely prolonged clinical course, and as a consequence are justly considered very low grade. This argument is often used to oppose aggressive attempts at cure. We are all acquainted with those patients who have lived with their disease in its various forms for from ten to twenty-five years. Yet many of us are not aware that many of these patients do die of their disease. In this series of patients with papillary tumors, 24 are dead of their disease. Of those patients who were followed for five or more years, 18, or 21 per cent are dead of disease. Of those who are dead of thyroid cancer, our estimated interval from the time of histologic diagnosis to death is forty-eight months. The

cause of death in many instances was due to local invasion of the larynx, trachea, esophagus, etc. Sixteen patients or 11.5 per cent developed chest metastasis at some time during the period of observation (9 on admission and 7 subsequently). Some of these patients with chest metastases are living and have remained asymptomatic for remarkably long periods of time. Nine patients, or 6.5 per cent, developed bone metastasis (4 on admission and 5 subsequently). Such lesions were often associated with other generalized manifestations of the disease which led to death. In addition to the one patient who had had enucleation of an eye prior to admission (which incidentally established the diagnosis) another developed an intraocular metastasis while under observation. Metastasis to the brain occurred twice. In one case the metastasis lodged in the choroid plexus and was removed, with apparent cure. The other terminated fatally.

The response to treatment: This, in many instances, was far from satisfactory. Many patients were inoperable on admission. In others, irradiation was used in conjunction with surgery. In 80 patients in whom irradiation was used alone, or in conjunction with surgery, there was no evidence of beneficial effect in 33, or 41.2 per cent. In 27 other patients, or 33 per cent of the group, there was some temporary improvement without ultimate control of the disease. Of the 10 patients who had prior thyroidectomy plus postoperative irradiation, all had recurrent or residual disease on admission. Four patients were referred to us for postoperative irradiation after subtotal thyroidectomy performed elsewhere. All of these patients have remained well. Although we have not attempted to set up a controlled series of cases, we feel that the value of routine postoperative irradiation may have been overemphasized. Its value is not apparent from the material in this series, but in 8 patients it appears that there has been arrest of the disease for long periods of time and that "cures" may indeed have resulted.

Evaluation of the results of radical surgery in this series of papillary tumors cannot be made at the present time, since this approach to the treatment problem has not been in effect for a sufficient period. Much of the material, even though followed for five years or more, is considered immature. This attitude toward therapy has been taken in the hope that radical surgery will add to the number of long-term cures. The failures of irradiation and limited surgery are frequent enough to justify more aggressive efforts. Subtotal thyroidectomy apparently has failed to cure many papillary tumors. This seems to be accounted for by the infiltrative nature of the tumor and the not uncommon finding of multiple foci of tumor in one or both lobes. Local excision of nodes does not seem reasonable to us. If surgery is to be used in an effort to effect permanent cure, we believe that it must be designed to remove all tumor-bearing tissue.

Follicular and alveolar carcinomas

There were only 22 tumors of this type in the series. Although follicular or alveolar structures make up a part of most thyroid tumors, very few pure tumors of this type are seen. This feature is so often overshadowed by other structural qualities that the predominant feature makes the tumor fall more naturally into other groups. Fifty-nine per cent of these tumors occurred in females. The median age was 45 years with the oldest being 74 and the youngest 9 years. Two-thirds of this small group had a history of a pre-existing goiter, and each of these patients had had a goiter for over one year. The average duration of goiter seemed to be no longer in this group than in others, since half had had goiters more than six years. Fifteen or 68 per cent had received treatment before coming to our clinic. Such treatment consisted of thyroidectomy with or without postoperative irradiation in 10 cases. The remainder had undergone miscellaneous procedures such as biopsy, or local excision.

On admission one usually finds these tumors occupying one lobe of the thyroid. They are frequently 3 to 4 cm. in diameter, but some may be quite large. In the absence of metastasis they are apt to present clinically as benign adenomas or nodular goiters. The tumors are usually encapsulated. Ten patients had osseous metastasis on admission. In fact, the primary lesion was not suspected in numerous instances until there was either pathologic fracture or bone pain. There was regional node involvement in 8 patients on admission and in 1 there was mediastinal node enlargement. Symptoms of hoarseness, dyspnea, dysphagia and weight loss were uncommon.

Clinical course: After follicular tumors are treated surgically, their clinical course often covers many years. Many of these tumors are not diagnosed by the pathologist after operation, due to their extremely orderly structure and the true nature of the process is not recognized until a metastatic deposit occurs in a bone or other distant focus, months or years later. Such cases comprise the group of so-called benign metastasizing strumas. They should be regarded as orderly follicular carcinomas. In addition to the patients who had osseous metastasis on admission, 2 additional patients developed this complication during their period of observation. Thus 45.4 per cent of the follicular tumors had metastasized to bone on admission and 54.5 per cent exhibited this feature during the period when they were under our observation. Nine of these patients are already dead of their disease and of the 3 still alive, 2 have marked disability, four, and nine and one-half years respectively, after the onset of their metastasis. One patient is living and asymptomatic twenty-two years after her thyroidectomy, and thirteen years after the onset of her bone lesions. In spite

of the reputed long history of the disease in patients with this type of tumor, those patients who died, did so on an average of thirty-seven months after the establishment of the diagnosis.

Response to treatment: The results of treatment have not been particularly good as far as the long-term picture is concerned. Of those followed for five years in our clinic, only 28.6 per cent are alive and well. Although the local disease is often curable by surgery, distant metastasis often causes the death of the patient. The response to irradiation has been variable but generally poor. Sometimes the pain from osseous metastases is ameliorated and pathologic fractures have healed under light doses of irradiation.

Solid adenocarcinomas

This group of tumors is the second most common form of thyroid cancer. There were 56 solid carcinomas in this series. The histologic picture in these tumors is very variable and seldom homogeneous in a single tumor. They are designated as solid, due to their habit of more or less indiscriminate growth in masses or columns with little or no tendency to form gland-like structures or papillary processes. All such tumors are associated with a high degree of malignancy. Only 55 per cent of the tumors occurred in females. The median age was 49 years; the oldest patient was 76 and the youngest was 16 years old. Forty-six or 82 per cent of the patients with the solid tumors gave a history of pre-existing goiter. Whereas 14 of these 46 patients stated that their goiter had been present for less than one year, 12 had known of their goiter for from ten to twenty years or longer.

On admission these bulky tumors were often found to involve more than one lobe. They were unencapsulated, densely hard, and due to their infiltrative nature, often extended beyond the limits of the gland. Obstructive symptoms were common and gastrostomy was required in 2 patients. One-half of the patients had node metastases on admission and in 1 there was pulmonary metastasis. Bone lesions were present in 7 patients on admission.

One-half, or 28 patients out of the group, had *received previous treatment* before coming to us and 17 of them had been subjected to subtotal thyroidectomy. Although most of the previously treated patients had prompt recurrence after prior surgery, 1 came to us twelve years after her original operation.

Clinical course and end results: The end results of treatment in the group of solid adenocarcinomas are depressing. In 25 per cent, osseous lesions developed during the course of observation. These were commonly associated with other metastatic deposits in the viscera. Death due to obstruction of either trachea or esophagus was common. The duration of life from diagnosis to death in those ending fatally was 26.4 months. Twenty-three

per cent of the patients followed five years or more were alive and free of disease. Irradiation did not influence the course of this type of tumor.

Hürthle cell carcinomas

A highly specific histologic variety of tumor is the Hürthle cell carcinoma, and this rarely offers a problem in diagnosis. Clinically these tumors are apt to be encapsulated and simulate a benign solitary adenoma. Whereas most of them are fairly small, about one-third are in excess of 6 cm. in diameter. One-quarter of the patients were males. The median age was 50 years; the youngest patient was 21 and the oldest was 67 years old. Of the 24 patients who gave a previous history of goiter, 25 per cent had had their tumors less than one year.

Fourteen patients, or slightly more than one-half, had received prior treatment which consisted of thyroidectomy in 9 patients. Three more had thyroidectomy plus postoperative irradiation.

Findings on admission: Eleven of the previously treated patients had no evidence of disease locally on admission. The others had chest metastasis. In the untreated cases the primary tumor was often encapsulated and mistaken for benign adenoma. This diagnosis was made in 8 out of 13 patients. Although none of these 8 patients had clinical evidence of metastases to cervical lymph nodes, dissection was done on the basis of frozen section and involved nodes were found in 6 of the 8 patients. They subsequently proved to be bilateral in two of these patients.

Clinical course: In patients with Hürthle cell cancer of the thyroid the clinical course is apt to be prolonged. In the fatal cases the average duration of life from diagnosis to death was 59.7 months. Osseous metastasis occurred in 5 patients of this group either before or after admission to our clinic. Pulmonary and osseous metastasis seemed to account for the majority of deaths in the group.

End results: While the Hürthle cell cancers have often been thought to be of a fairly low grade of malignancy, the end result does not bear this out. Only one-third of the patients falling into the five year follow-up series were alive and free of disease for this period of time.

Giant cell tumors

There were 39 giant cell tumors in this series of patients. The median age for the group was 61 years, which is considerably greater than that for the group at large. The youngest patient was 34 years old and the oldest was 86, which is also the oldest recorded age for the entire series. Thirty-three of the 39 patients gave a history of pre-existing goiter and in 18 of those giving such a history the goiter had been present less than one year. Twenty-one of the patients with a giant cell tumor did not give a history

of any previous treatment. Of those patients who had been treated before coming to us, 9 had had thyroidectomy and 9 others had had biopsy only. Those patients who had been irradiated previously had shown no response.

Findings on admission: These very bulky tumors were notable, on admission, for their local extension in the neck. They were highly infiltrative and were said in some instances to have given the patient a "bull-necked" appearance. Almost one-half of these patients presented evidence of regional lymph node involvement on admission and in 5 the nodes were bilateral. The late symptoms of hoarseness, dyspnea and dysphagia were present on admission in almost one-half of the patients in this group.

Clinical course: Rapid progress of the disease is the outstanding characteristic in the clinical course of giant cell tumors. Death is often due to obstruction of the trachea or esophagus, or both. Although visceral metastases did occur, death usually intervened before this complication had a chance to develop. All of these patients are dead. Thirty-eight of them died of their cancers, and 1 of unknown cause. The average duration of life from diagnosis to death was approximately 4.8 months. It would appear that in no other form of human cancer is such a certain lethal outcome so inevitable. Bone metastases occurred three times in this group of patients.

Results of treatment: As indicated in the preceding paragraphs, the results of treatment were most depressing. We attempted surgery in only 4 of the patients not previously treated and were unsuccessful in our efforts each time. We were able to do radical surgery in 1 patient who had been subjected to prior biopsy. This patient, however, was dead within one year. The response to irradiation was uniformly negligible.

SUMMARY

Three hundred and one cases of thyroid cancer have been reviewed. An effort has been made to trace the natural history of the disease in relation to the histologic types. Although 215 of these patients have been followed for five or more years, it is pointed out that the five-year yardstick as a criterion of cure may be of limited value in some forms of thyroid cancer. Since 38.6 per cent of the patients represent prior-treatment failures on admission, the authors conclude that a more radical approach to the treatment of thyroid cancer is indicated.

WHEN IS MALIGNANT GOITER MALIGNANT?*

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IN any discussion of malignant goiter there is always a question as to just what the author means by malignant goiter. In the literature for the past twenty-five years, and especially in the discussions which have taken place before this Association and other scientific organizations, there is considerable controversy as to whether this or that lesion should be included in the group under discussion, whether this or that pathologic criterion is definitive in the determination of malignancy, whether pathologic or microscopic findings alone can determine malignancy or whether the diagnosis can be reached only on a clinico-pathologic basis. My thesis is that only by clinical study, painstaking pathologic investigation and by a long personal follow-up can it be determined whether some of the more controversial cases are malignant or not. It is with the hope of answering some of these questions that the following study of 178 cases is presented.

Group I

First of all there are cases in which there is no doubt of the presence of malignancy. This is the group of highly malignant tumors, undifferentiated microscopically, rapidly growing, invasive locally and prone to metastatic involvement of the lungs or other distant regions. These tumors seem insensitive to radiation therapy, prone to postoperative recurrence and uniformly prove rapidly fatal. Incidentally, death from the tumor or its metastases is the final incontrovertible proof of malignancy. A few examples of this group will serve to illustrate the point (Fig. 1). There were 48 (27 per cent) of these patients in my series and they are all dead of the disease, with an average length of life of seven months from the time of diagnosis. Nobody will question malignancy here. These tumors prove their nature in rapid order by killing their hosts. Incidentally, there is one pathologic finding of grave prognostic import in these cases, namely, polymorphonuclear infiltration as seen in some of the microscopic sections (Fig. 1, C and E). So much for the noncontroversial group.

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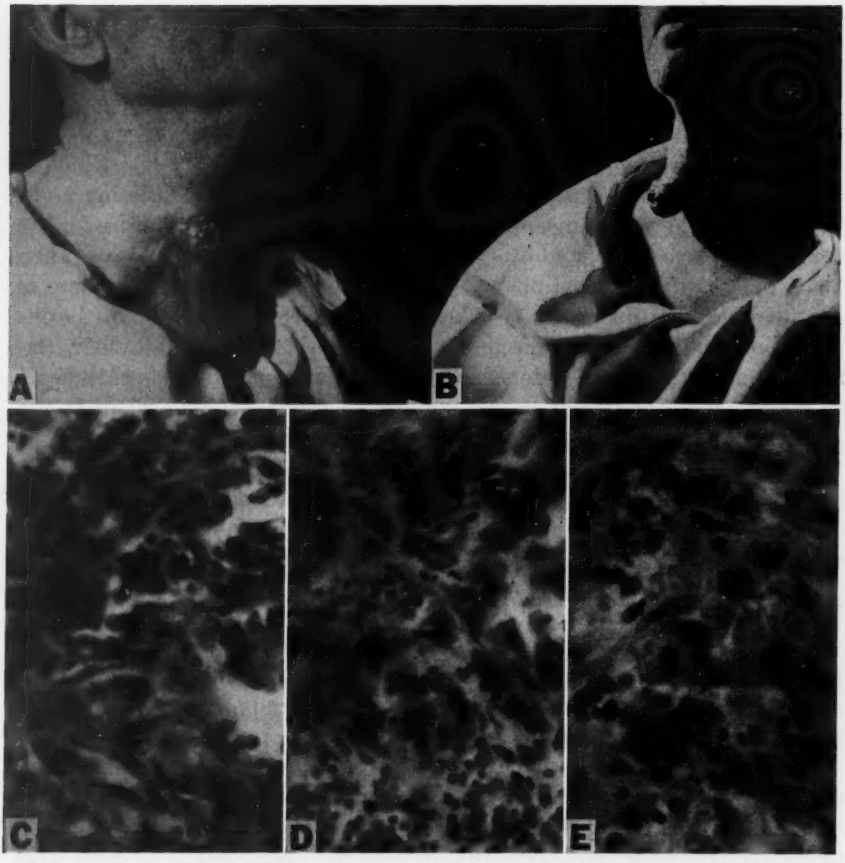

FIG. 1. Examples of highly malignant, rapidly fatal cases. *A* shows a lateral view and *B* a front view of the goiter in Patient #68* who died three and one-half months after this photograph was taken, with massive pulmonary involvement. *C* shows a section of tumor from the same patient. *D* shows a section from the tumor in Patient #16 who died two months after operation. *E* shows a section from Patient #65 who died five and one-half months after operation. (All sections ×450.)

* In this and subsequent figures, the case number is that used for the patient in an earlier study (1).

Group II

The first controversial group I wish to discuss is the so-called "benign metastasizing goiter." This group is controversial only because of Cohnheim's original conception that there could be such a thing as vascular transportation of normal thyroid tissue and its growth as a benign tumor

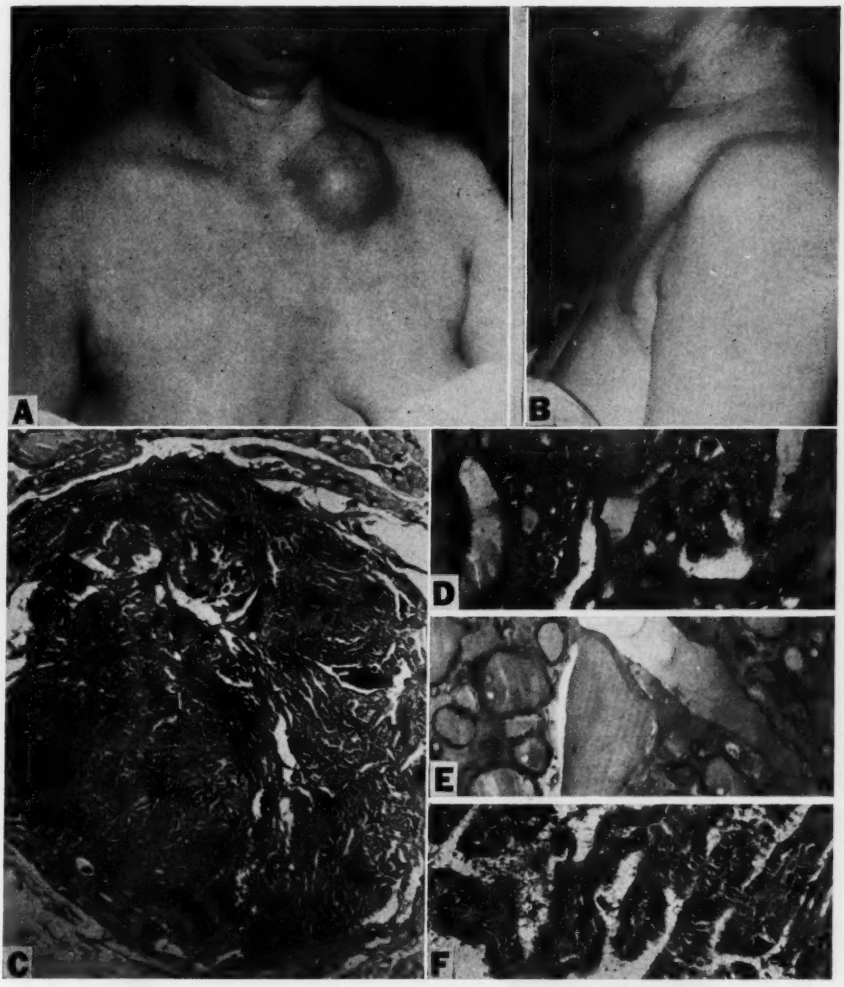

FIG. 2. C. K., case 118. Malignant goiter, the primary lesion of which was discovered only after removal of clavicular tumor had shown it to be of thyroid origin. *A* and *B* show original clavicular tumor; *C* shows entire primary tumor of the left lobe of the thyroid gland (×30); *D* and *E* show sections of the growth from the clavicle (×120); and *F* shows a section of the primary tumor (×120).

in some place distant from the thyroid gland. His theory was lent some credence by the finding of thyroid tissue of apparently normal microscopic structure in these metastatic lesions and the failure to find its place of origin as a minute malignant tumor of the thyroid gland. Later investiga-

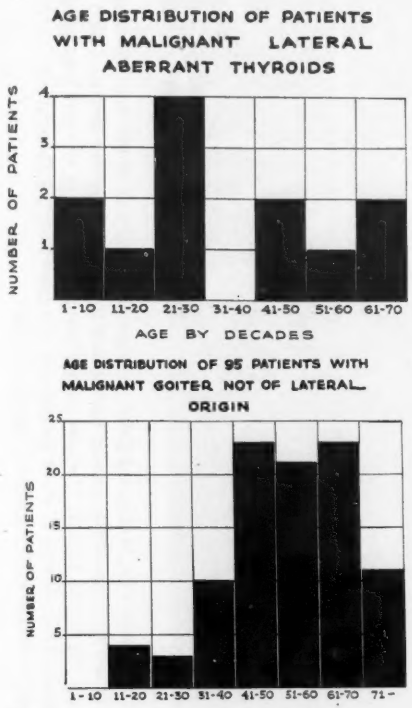

FIG. 3. Graphs illustrating early age at which cancer of aberrant thyroid tissue occurs as contrasted with that of midline origin.

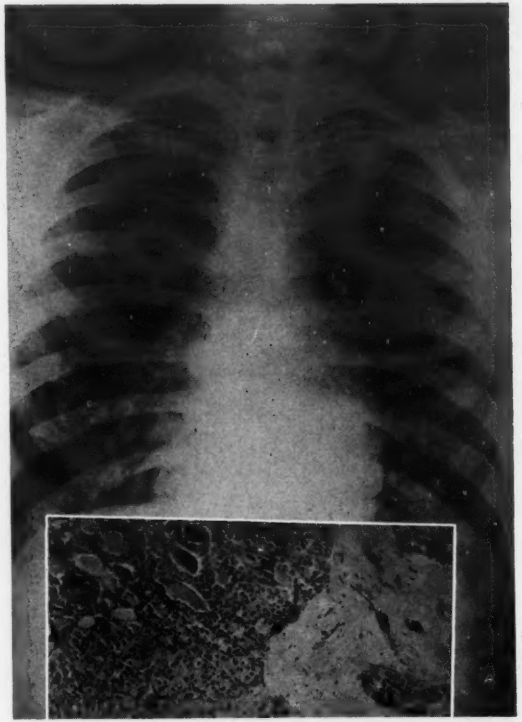

FIG. 4. Roentgenogram of J. R. E. (case 42) taken at the age of 8 years 10 months. There has been no change in this picture in nineteen years. Insert shows section of tumor (×80).

tions have shown that the original focus of malignancy can be found, although often requiring the most careful serial section of the entire thyroid gland. One illustrative case is presented in Figure 2. This patient, C.K., a woman of 43, had an excision of the left clavicle for the tumor shown in the illustration, on June 20, 1940 (Fig. 2, A and B). The clinical diagnosis was chondroma. When the tumor was found to consist of thyroid tissue, some of which was microscopically normal in appearance (Fig. 2, D and E), a more careful examination of the thyroid gland revealed a hard nodule about 1 cm. in diameter in the left lobe. This was considered to be the origin of the clavicular metastasis. Following a lobectomy done July 31, 1940, the palpable nodule was found to be a benign, encapsulated, calcified nodule whereas the malignant tumor from which the metastasis had originated was only 5 mm. in diameter. The latter is shown completely in Figure 2C, and in section in Figure 2F.

This group can then be eliminated from the controversial class by stating that any tumor that metastasizes is malignant, and that the focus of origin will be found if the thyroid is obtainable and is examined carefully by serial section. I am sure we can all report cases in which the metastases were the presenting pathologic entity and in which the tumor of the thyroid remained dormant for years or until discovered at autopsy. There were 7 such cases in my series, an incidence of 4 per cent.

Group III

Another group in which there is controversy over the presence of malignancy is that of the so-called lateral aberrant thyroid tumors. As has been previously shown (1) there are certain characteristics of this group which do not fall into the pattern of malignancy in general. In the 15 cases previously reported by me, the peak of incidence was below the age of 30, whereas for carcinoma of the thyroid it was in the decades between 40 and 70 (Fig. 3). Moreover, the microscopic criteria of malignancy are especially ill-defined in this group. Papillary cyst adenomas or solid sheets and bundles of cells with little tendency to invade, scarcity of mitotic figures, and minimal dedifferentiation are characteristic of these tumors. Whether these growths are all metastases in the cervical lymph nodes from a primary thyroid carcinoma, as some authors hold (2), or are growing fetal rests with little or no evidence of malignancy, as claimed by other investigators (3), the fact remains that in many instances they do not follow the pattern of the more definitely malignant tumors and there is often a question of the actual existence of this condition in the individual tumor. Because the malignancy of many of these cases is of such a low degree, the proof of its actual presence must often await years of follow-up.

Three examples of this type are presented here (J.R.E., J.W., and E.F.).

The first was a boy who was 8 years and 10 months of age when first seen and operated upon. He is now 27 years old and despite the early positive findings in his chest (Fig. 4) the only sign of invasion shown by his tumor was erosion into the pharynx at the age of 22. This process has now been controlled by a therapeutic dose of radioactive iodine. Incidentally, he is the one case in this series showing an uptake of I^{131} in sufficient amount to give therapeutic results. You may well say that there is no question of the malignancy of this tumor. However, I should like to point out that it took fourteen years to prove it and, moreover, the lesions in the lungs have not progressed in the nineteen years that this patient has been under observation.

FIG. 5. Diagram showing location of nodules in J. W. (case 36). Insert shows section of tumor (×450). There has been no recurrence in nineteen years.

The second case (J.W.) is that of a girl who was operated upon at the age of 16. The diagram (Fig. 5) shows the distribution of nodules in her neck. The lowest was in the thyroid gland. She is now 35 years old, has raised a family and has never shown signs of recurrence. Has time proved this to be a benign condition or was this patient cured of a malignant tumor by partial thyroidectomy, radical neck dissection and postoperative radia-

tion? Or is nineteen years of freedom from recurrence, a proof of cure?

The third case (E.F.) is one of a woman aged 52 when first seen. It is possible that she does not legitimately belong to the group of lateral aberrant tumors but she does, nevertheless, show the value of prolonged follow-up in the determination of the presence and degree of malignancy. One month after a biopsy diagnosis, a radical neck dissection was performed, as shown in Figure 6. The tumor was predominantly of the cystic-papillary type (Fig. 7 C) and the patient remained well and without apparent recurrence for four years following operation and x-ray therapy. Four years later a barely palpable recurrence below the scar disappeared following a second course of irradiation. She remained well for almost seven years and then she developed a Horner's syndrome from involvement of the cervical sympathetics by a process which gave no palpable evidence of its presence. There was a favorable response to radiation, as shown by diminution of the Horner's phenomenon. A few months later she died after an acute illness of three days. Death was due to collapse of the left lung, the pleura of which was studded with innumerable deposits of a completely undifferentiated carcinoma as shown in Figure 7, A and B. That this was an environmental variation of the original papillary tumor of the neck was demonstrated by the maintenance of the papillary form in the depths of the lung (Fig. 7 D). Here, then, is a case in which only the *degree* of malignancy of the tumor was in question. It may serve to explain how some of these low-grade malignancies can remain dormant for years and then become completely unmanageable when a new factor or new location removes the tissue resistance which has kept them under control for long periods of time.

FIG. 6. E. F. (case 20), showing extent of neck dissection.

Group IV

Next we come to that much larger and more important group of thyroid tumors in which the diagnosis hinges largely on the microscopic picture. There are two types of tumor in this group. In one, the tumor demonstrates

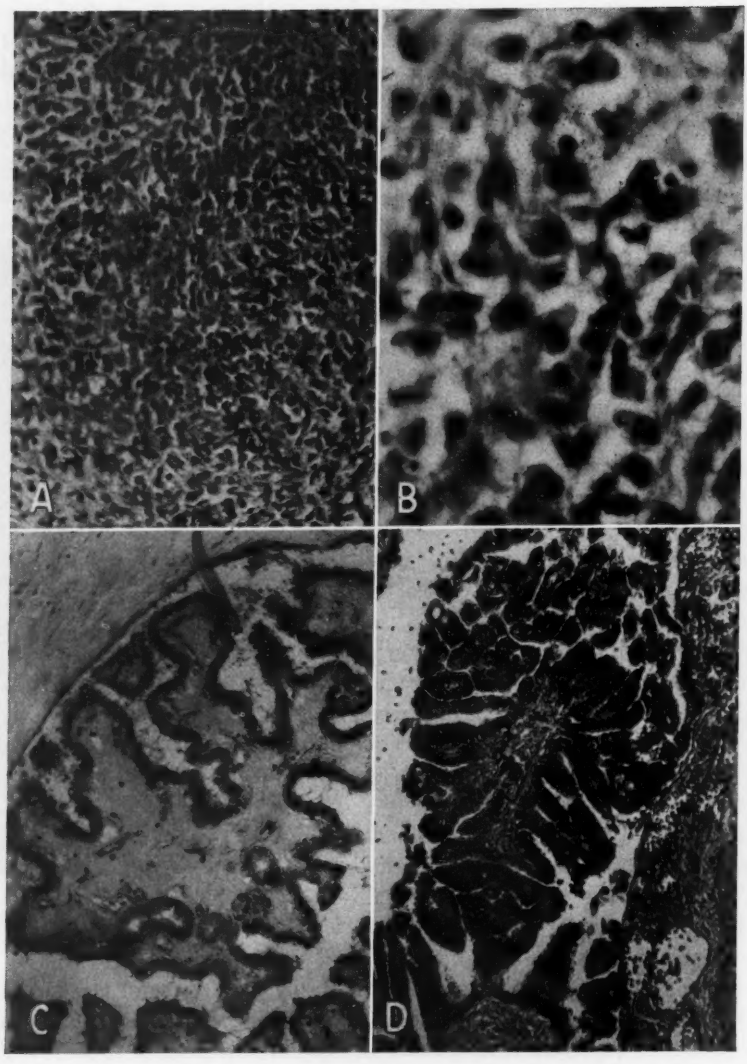

FIG. 7. Microscopic sections from E. F. (case 20).

A shows a section from an undifferentiated tumor of the pleura found at autopsy (×20).

B shows the same section (×500).

C shows a section from the original tumor showing cysto-papillary pattern (×120).

D shows a section from the hilus of the lung at autopsy, showing same papillary pattern as original tumor (×120).

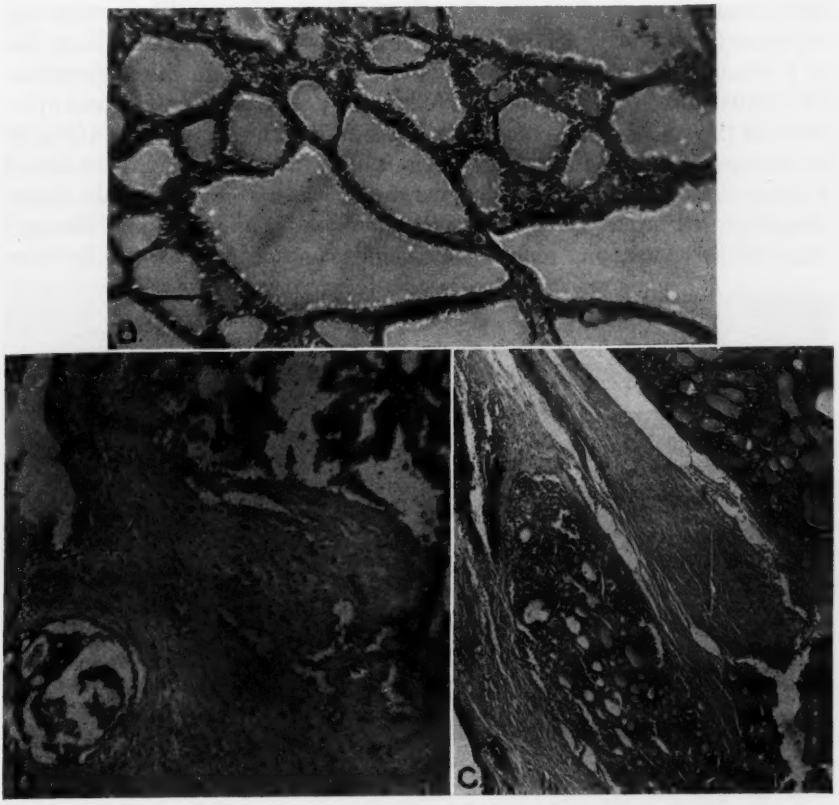

FIG. 8. Microscopic sections (×150) from P. L. (case 82). a.) Normal-appearing thyroid, typical of tissue from first recurrent nodule. b.) Papillary tumor with lymphatic invasion shown in specimen taken at last operation. c.) Questionable capsular invasion which, coupled with clinical history, led to diagnosis of carcinoma after second recurrence.

its malignancy by repeated recurrence after local removal but the pathologic examination fails to confirm malignancy. In the other, there is either abundant or questionable microscopic evidence of malignancy but the clinical findings and course fail to correspond.

An example of the first group is to be found in a woman (P.L.) who developed a goiter during the course of pregnancy at the age of 24. The goiter remained static for twenty years and then at the age of 44, began to grow. She was first operated upon at the age of 50 and again, for local recurrences, at the ages of 54 and 58. No microscopic evidence of malignancy was demonstrable upon careful pathologic examination of the speci-

men obtained at the first two operations. Very questionable microscopic evidence (Fig. 8), coupled with the clinical history and gross findings, led to a presumptive diagnosis of malignancy following the third operation. This patient had roentgen therapy followed by recurrence and radical operation at the age of 63 and finally died of skull and lung metastases (Fig. 9) at the age of 68. The following questions arise in this case: Was the tumor malignant from the time of its appearance at the age of 24? Did the beginning of growth twenty years later at the age of 44 signify malignant change? Was the first or second recurrence an indication of loss of tissue defenses

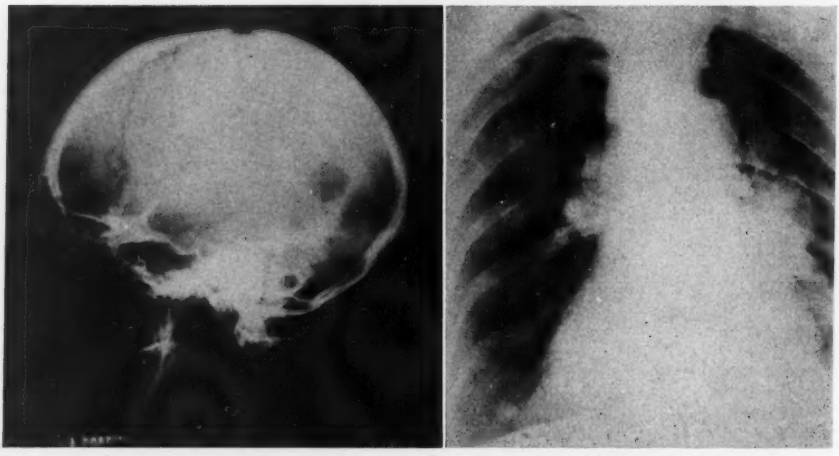

FIG. 9. Roentgenograms showing skull and lung metastases in P. L. (case 82) shortly before death, forty-four years after development of original goiter.

against a previously dormant malignant neoplasm? There is one thing certain about this case, namely, that time and a careful follow-up were necessary for incontrovertible proof of malignancy—death from metastases. The history in this instance covered a span of 44 years.

Group V

Finally we come to the other side of the picture in the most important group of all, namely, those cases in which a presumptive diagnosis of malignancy is made by the pathologist on the basis of gross and microscopic findings but the clinical course is that of a benign tumor. It is in this group that all the criteria developed by the pathologist are put to the acid test of time. It is particularly in this group that cures can be sought and striven for with a high degree of hope. It is in this group that the obtaining of a hoped-for cure throws doubt upon the original diagnosis. And it is in this

group especially that the alert physician, basing his advice upon statistical analyses, can look for the greatest opportunities of salvage and reduction in loss of life from this disease.

Among students of the subject it has long been recognized that the criteria of malignancy in tumors of the thyroid are much less dependable than in other organs. Graham (4) found blood vessel invasion indicative of malignancy in adenomas and later Warren (5) reported that only 6.3 per cent of his cases in which blood vessel invasion was found ran a malignant course. It would be presumptuous of me to discuss the cytologic and other microscopic criteria of malignancy when the pathologists, the final arbiters, will often disagree. I can only emphasize the importance of a prolonged painstaking follow-up program in helping to solve the problem. I know it will be interesting to you to know what the passage of twenty-five years has done to answer some of these questions for us.

Eliminating all living patients who were seen within the last five years there were 178 cases included in this study. Twenty-two of these were first diagnosed as malignant in the laboratory. Of these 22, 1 died from recurrence in thirty-two months, 1 is living with recurrence seven years after diagnosis, and 4 died without signs of recurrence at five months, eight years, seventeen years and eighteen and one-half years respectively after diagnosis. Sixteen are living and well five and one-half to twenty-five years since diagnosis and the average length of postoperative life is eleven and one-half years.

When we compare these living patients with the 19 living patients who had both pathologic reports of cancer and clinical evidence of malignancy as shown by operative findings, we find that all of the patients who survived have lived from six to twenty-five years and that the average length of life has been exactly the same in each group—eleven and one-half years.

SUMMARY

In some tumors of the thyroid gland, only by years of follow-up can we answer the question of malignancy. In the cases cited here, doubt as to the presence of malignancy was raised only by the long survival of the patients. If the patients had not been carefully followed for long periods of time the diagnosis would not have been questioned. It was most interesting to find the same average length of life after diagnosis made by clinical-pathologic means as after diagnosis made by pathologic criteria only. It indicates the value of studies in which the statistics point a finger of suspicion at certain groups of thyroid tumors which must not go untreated if we hope to increase the number of cures in this disease. As more of these tumors are removed because they fall in the suspected group, there will be an increasing number of cases in which malignancy is doubtful on the grounds of long

survival: but, by the same token, there will be an increasing number of people who survive because their cancer was cured by early operation.

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LYMPHOSARCOMA OF THE THYROID*

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LYMPHOSARCOMA of the thyroid is infrequently reported. In a twenty-two year period (1924 through 1945) 8 patients with this disease were operated upon at the Cleveland Clinic. Because of the paucity of reported cases of lymphosarcoma of the thyroid in the literature, this series will be presented here.

Pool (1) in 1927 reported 2 patients with lymphosarcoma of the thyroid who died within eight months of the time of local extension. Means (2) has seen 3 cases in which lymphosarcoma appeared to arise in the thyroid gland. Hertzler (3) felt that lymphosarcomas of the thyroid were most distinctive and definitely not epithelial in origin. Graham (4) stated that many cases reported in this country as small cell carcinomas are in reality lymphosarcomas. Some of these appear to be remarkably responsive to irradiation, and some persons who have this disease may survive for many years. Anderson (5) on the other hand, warned that small cell carcinomas of the thyroid are easily mistaken for lymphosarcoma. Karsner (6) emphasized that care must be taken to distinguish lymphosarcoma from small cell carcinomas. Crotti (7) agreed that, in accordance with the more recent observations, the round cell carcinoma was to be regarded as a lymphosarcoma.

DeCourcy (8) felt that lymphosarcomas of the thyroid are similar histologically to this type of neoplasm in other organs and have the same developmental characteristics and clinical course. They grow rapidly and are usually in advanced stages before therapeutic procedures are instituted. These tumors are not surgically curable and although they are radiosensitive, good results are seldom obtained by roentgen treatment. All 4 patients in Pemberton's series (1939) of 774 cases of malignant lesions of the thyroid died within one year after operation.

Stout (9) admitted that generalized sarcoma and sarcoma-like lesions occurred in the thyroid gland. He mentioned 1 case of lymphosarcoma in which the thyroid gland, as well as many other organs and tissues, was involved.

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Ewing (10) however, was opposed to the above views and flatly stated that the occurrence of true sarcoma of the thyroid in man requires demonstration. He further added that Braun's lymphosarcoma of the thyroid presented none of the distinguishing features of this disease. Bell (11) stated that most sarcomas of the thyroid are metaplastic carcinomas. Boyd (12) agreed that most, if not all, sarcomas of the thyroid are anaplastic carcinomas.

CLINICAL MATERIAL

As shown in Table 1, the sex incidence of the 8 lymphosarcomas of the thyroid was 8 in women and none in men. The average age of the patient at the time of surgery was 57.5 years, the youngest being 30 years and the oldest 75 years of age. In only 1 case was there a goiter present for many

TABLE 1. LYMPHOSARCOMA OF THE THYROID, 1924–1945

Case No.	Age (yrs.)	Sex	Clinical history	Preoperative diagnosis	Surgery—date	X-ray therapy	Length of time between operation and death
1*	56	F	Rapid enlargement of neck, 2 mos.	Carcinoma	Right lobectomy	0	4 mos.
2	60	F	Goiter 38 years. Rapid enlargement and dyspnea, 4 wks.	Carcinoma	Thyroidectomy-tracheotomy, 6-26-27	0	1 mo.
3	30	F	Enlargement of neck and dyspnea, 2 mos.	Carcinoma	Thyroidectomy, 12-31-27	+	4 mos.
4*	41	F	Thyroidectomy Oct. 1928. Rapid enlargement of neck, 3 mos.	Carcinoma	Right lobectomy, 7-15-29	+	5 mos.
5*	72	F	Enlargement of neck, 6 wks.	Carcinoma	Left lobectomy	+	6 mos.
6	59	F	Pain, dyspnea tight feeling in neck, 1 mo.	Thyroiditis	Thyroidectomy, 5-3-33	+	3 mos.
7	67	F	Rapid enlargement, pain radiating to ear, and dysphagia, 5 wks.	Carcinoma	Pyramidal lobectomy for decompression, 7-24-34	+	3 mos.
8	75	F	Swelling right side of neck, 2 wks.	Carcinoma	Right lobectomy, 11-16-36	+	7 mos.

* Cases 1, 4 and 5 had preoperative unilateral vocal cord paralysis.

years. In this instance there had been a recent rapid increase in size of the thyroid gland over a six-week period. All other cases presented a recent enlargement of the thyroid of from seven weeks to six months' duration. Two patients complained of difficult breathing and 1 of dysphagia. Of the

6 patients who had a preoperative vocal cord examination, 3 had unilateral vocal cord paralysis.

In 7 cases malignancy was suspected and in 1 case thyroiditis was the preoperative diagnosis. X-ray examination of the chest preoperatively in 4 cases showed no pathology. In 4 cases no chest roentgenogram was recorded.

In 4 cases lobectomy was performed; in 3, thyroidectomy; and in 1 case, pyramidal lobectomy for decompression. Cervical lymphadenopathy was not present clinically or at operation. All but 2 patients received roentgen therapy postoperatively. All 8 patients died within seven months after operation, with an average survival time of four months.

During the period of this survey over 15,000 patients submitted to thyroid surgery at the Cleveland Clinic. These cases of lymphosarcoma include only those tumors of lymphocyte origin. Plasmocytomas, reticulum cell sarcomas and other neoplasms of the lymphoblastoma group are to be reported separately.

PATHOLOGY

The diagnosis was based on massive involvement of the thyroid gland and upon the presence of the lymphocyte or the lymphoblast as the cell of infiltration. Instances in which the diagnosis must be based on biopsies of tissue about the thyroid have been excluded, due to the fact these might possibly have been cases of infiltration of the gland by lymphosarcoma of nearby structures.

Gross appearance: The specimens received consisted of irregular masses of tissue or the greater portion of an identifiable lobe of thyroid. The specimen weights varied from 28 to 400 grams. As a rule only small islands of thyroid tissue or adenomas could be recognized. Sufficient thyroid however was apparent to call for a diagnosis of nodular goiter in half of the specimens. In 1 instance a large adenoma was encountered and it was partly infiltrated by the neoplasm. The thyroid capsule was at least partly invaded in all specimens, infiltrated muscle being found in one. A smooth tracheal depression could be identified in 1 instance although a capsule was not evident. The tumor tissue was firm in consistency, tough and occasionally elastic. The cut surfaces were pale gray, yellow gray or white, in 1 instance showing purplish red patches and in another brownish red. Surfaces were usually smooth on section, occasionally bulging slightly. One specimen presented a somewhat striated appearance.

Microscopic appearance: The thyroid tissue in 1 instance presented a histologic appearance compatible with struma lymphomatosa insofar as it could be determined from the available remaining anatomic structure. In 4 instances the thyroid structure was definitely nodular; in a fifth there

was slight nodule formation and moderate fibrosis; and in a sixth there was slight hyperplasia of the follicles and fibrosis. Thyroid tissue occurred only as a few scattered islands within the tumor in 2 cases. Neoplastic infiltration occurred in broad areas, completely replacing thyroid parenchyma or engulfiing isolated follicles singly or in groups. In 1 instance there was a moderate increase in connective tissue stroma; in all others, a sea of neoplastic cells. Cells for the most part were of typical small lymphocyte type, except for some irregularity of the dark-staining nuclei. However, occasionally there were patches of and individually distributed typical lymphoblasts or immature forms. No tumor giant cells were found. Zones of necrosis were present in 1 case. Mitoses varied from a moderate number to numerous. Reticulum stains revealed no reticulum fibers surrounding individual tumor cells or cell groups. In all instances fat and fibrous tissue adjoining the section of thyroid revealed diffuse infiltration by the neoplastic cells. Muscle was infiltrated in the case in which a portion was removed with the thyroid. Frequently blood vessels, usually veins or venules, revealed a thickening of the intima due to infiltration by neoplastic lymphocytes. Occasionally small endothelial-lined spaces contained loose masses of lymphocytes.

Differential pathologic diagnosis: The two lesions of greatest importance in regard to differential diagnosis are undifferentiated carcinoma of small cell type and struma lymphomatosa.

Although the cell size in small cell carcinoma may approach that of lymphosarcoma, the arrangement of the cell units, at least in some part of the tumor, is cord-like or sheet-like rather than like that of diffuse single cell infiltration. Reticulum production is therefore evident about single groups of cells. Another feature is the absence of the diffuse subendothelial infiltration by tumor cells as seen in lymphosarcoma. Intravascular extension is manifest in carcinoma by masses of neoplasm within the vessels and though these masses may in part have endothelial covering, the uniform intimal infiltration present in lymphosarcoma is not found.

Rarely struma lymphomatosa presents such a diffuse and cellular infiltration as to cause considerable difficulty in differentiation from lymphosarcoma. The major features of diagnosis are as follows: in struma lymphomatosa, infiltration is most often limited by bands of connective tissue separating the thyroid plates, lymph nodules are usually prominent and well formed, the cell of the infiltrate is partly of the plasma cell type, and oxyphilic follicles are distributed through the infiltrate. One very important feature, which can be shown only when adequate tissue blocks are available, is the absence of infiltration of structures adjoining the thyroid in struma lymphomatosa.

SUMMARY

Eight cases of lymphosarcoma of the thyroid are reported. The course of the disease in all 8 patients was rapid demise within seven months, in spite of surgical and roentgen therapy. The pathologic aspects of the disease are outlined.

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TOTAL THYROIDECTOMY IN THE MANAGEMENT OF DIFFUSE TOXIC GOITER*

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IT is the purpose of this paper to present our experience with total thyroidectomy in the management of diffuse toxic goiter. This report reviews a series of 280 patients operated on by one-stage procedures during the fourteen-year period from 1935 to 1949. We feel that total thyroidectomy offers a rational surgical approach to the problem and that it may eliminate certain inadequacies of subtotal thyroidectomy.

In 1939, Scott (1) presented before this Association a preliminary report on 71 total thyroidectomies, wherein he outlined the reasons which justified the procedure. We believe these statements to be just as applicable today as then and wish to recall the following points:

Many years ago, Henry Plummer (2) pointed out that the manifestations of exophthalmic goiter appeared to be due to a qualitatively abnormal secretion rather than to a mere excess of a normal thyroid secretion. Apparently little attention has been paid to this early premise. However, we still do not know the cause of diffuse toxic goiter and today, we, as did Plummer, can only speculate as to the true etiology of the disease.

If Plummer's premise is assumed to be correct, then it follows that so long as the thyroid gland or any remnant thereof remains *in situ*, it may secrete an abnormal substance capable of producing any or all of the manifestations of hyperthyroidism in varying degrees of severity. It should also follow that these manifestations can be abolished in one of two ways: 1) either the thyroid tissue producing the abnormal secretion must be converted to normal thyroid tissue producing a normal secretion, or 2) there must be complete ablation of all of the abnormal thyroid secretion.

We believe that Plummer's hypothesis merits reconsideration and that it may explain the persistent symptoms observed following subtotal thyroidectomy, since such a procedure leaves a remnant of abnormal thyroid tissue *in situ*.

It is a fact well known to all of us that persistent manifestations do occur following subtotal operations. They are noted as tachycardia, nervous excitability, fatigue, weight loss, exophthalmos, and numerous other symp-

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toms. Their incidence in a degree warranting further antithyroid treatment or operation is reported by various authorities as being from 2.3 per cent (3) to 17.5 per cent (4, 5, 6). In this series, 32 patients (12.3 per cent) had secondary procedures performed as the second, third, or fourth thyroidectomy.

If we acknowledge these recurrences, then we must also acknowledge that subtotal thyroidectomy is not an entirely satisfactory treatment for diffuse toxic goiter. The same may be said for medical management, including radiation, since it is generally conceded that these measures are associated with even higher recurrence rates following cessation of the treatment. This appears to be true of propylthiouracil as well as of drugs less recently introduced. Microscopically the thyroid tissue of patients treated with thiouracil and its derivatives displays a cytologic structure not unlike that observed in the untreated, highly toxic hyperthyroid patient. Available drugs are not capable of restoring the thyroid gland to normal and of so maintaining it.

Obviously, then, we cannot fulfill the first mentioned hypothetical requirement for the permanent relief of hyperthyroidism and there remains only the second stated idea of treatment, that is, the total ablation of all abnormal thyroid secretion. This can be accomplished by total thyroidectomy. If such a procedure can be carried out with a reasonable morbidity and mortality rate, then it should be worthy of consideration. We believe today, as we did in 1939, that we can perform total thyroidectomy with a morbidity and a mortality rate comparing favorably with those attendant upon subtotal operative procedures.

Total thyroidectomy was abandoned by Kocher and others in favor of subtotal procedures because of the complications and sequelae, particularly the postoperative myxedema. The operation was replaced by resection not because of any inherent superiority of the latter procedure, but because of the lack of knowledge and the lack of means to combat such conditions as 1) postoperative athyrea, 2) parathyroid tetany, and 3) recurrent laryngeal nerve injury. These circumstances initiated the trend toward subtotal thyroidectomy which has persisted to this day. It has been our observation that the incidence of the mechanical complications and sequelae in this series compares favorably with the incidence following subtotal thyroidectomy. We shall briefly consider our experience with these once prohibitive factors.

Postoperative follow-up

In this series of 280 patients, 269 (96.1 per cent) have been studied subsequent to operation, as noted in Table 1. Of this group, 78.9 per cent have been followed two years or longer. Only 11 patients (3.9 per cent) have not

been followed. Of the 269 patients traced, 256 comprise the basis for this report, since 7 were operated upon too recently to be included and 6 patients died.

TABLE 1. POSTOPERATIVE FOLLOW-UP

Number of patients	280	
Number of patients traced	269	96.1%
Number not traced	11	3.9%
Operated upon too recently	7	
Postoperative deaths	6	
Available for study	256	

Postoperative athyrea (myxedema)

Total thyroidectomy will convert a hyperthyroid patient into a hypothyroid patient unless proper medication is administered. Our experience dictates that an euthyroid state can easily be maintained by the oral administration of a fresh, standard brand of desiccated thyroid. For reasons previously published (1, 8), we prescribe Parke-Davis desiccated gland. However, other brands of thyroid will serve equally well, provided the difference in dosage is understood.

TABLE 2. POSTOPERATIVE ADMINISTRATION OF DESICCATED THYROID

Number of patients	Percentage of total	Daily dose in grains
17	6.6	½
180	70.3	1
36	14.1	1½
20	7.8	2
3	1.2	3
256	100.0	

Table 2 illustrates the daily oral dosage of desiccated thyroid taken by these athyroid patients. One hundred and eighty patients (70.3 per cent) require one grain daily and 36 patients (14.1 per cent) require one and one-half grains daily. Thus, we note that about 85 per cent of these patients are in these two groups. A mean average basal metabolic rate of minus 3 per cent is maintained by the dosages listed, as judged by most recent examinations. Variations in the dosage required apparently depend somewhat upon the weight of the patient.

There were 128 female patients in the child-bearing period of life. Subsequent to operation, 29 normal children have been born to patients in this group.

These facts further substantiate our belief that a normal status can be

maintained following total thyroidectomy by the proper administration of desiccated thyroid.

Parathyroid tetany

The majority of parathyroid disturbances in our series have been temporary in nature and easily controlled. These temporary manifestations apparently are due to a circulatory disturbance occurring during and after the operation and they subside in a few days. On the basis of this observation, we now routinely administer 100 units of parathyroid extract daily during the first five postoperative days. Since this innovation four years ago, no such temporary disturbance has been noted. Prior to this, 12 instances of transient tetany occurred. All of these patients were relieved by treatment before dismissal from the hospital.

TABLE 3. PARATHYROID TETANY

Type of tetany	Number of patients	Percentage of total
Transient	12	4.3
Chronic*	3	1.1

* Only 1 patient (0.36%) requires dihydrotachysterol (A T 10).

It will be noted in Table 3 that chronic tetany occurred in 3 patients (1.1 per cent). In all three, the disease is controlled by treatment. Two of these patients are maintained on oral calcium alone. It is questionable whether these 2 patients should be classified under chronic tetany since their symptoms are very mild, occur infrequently, and are controlled by oral calcium. In only 1 instance has dihydrotachysterol (A T 10, Winthrop) been required in the daily dosage of .625 milligram to maintain normal blood calcium levels. In no instance has there been a fatality from this complication and no chronic tetany has occurred since 1940.

Recurrent laryngeal nerve injury

We have noted a temporary disturbance of laryngeal function on 9 occasions. These are listed in Table 4 as transient nerve injuries, since the symptoms subsided in a few days and subsequent examinations have re-

TABLE 4. RECURRENT LARYNGEAL NERVE INJURY

I. Transient nerve injury	
9 unilateral	
II. Permanent nerve injury*	
2 bilateral	
2 unilateral	

* Incidence of permanent injury—1.4%.

vealed no evidence of permanent vocal cord paresis. We believe such disturbances result from operative trauma and the resulting edema in contradistinction to the actual severance or destruction of a portion of the nerve which apparently produces permanent vocal cord paresis.

Permanent nerve injury has occurred 4 times, an incidence of 1.4 per cent. Two of these injuries were unilateral; 2 were bilateral. All 4 of these were among the earliest patients operated on before our technique of protecting the nerve was well developed. No permanent nerve injuries have occurred since 1939, during which period 209 patients have been operated on by this procedure.

Postoperative rehabilitation

Table 5 indicates the postoperative rehabilitation. Two hundred and twenty-five patients (87.9 per cent) were classified as being euthyroid. Nineteen patients were regarded as having a good result although not entirely satisfactory, largely because of the patients' improper usage of desiccated thyroid. The condition of 12 patients (4.7 per cent) was regarded as definitely unsatisfactory. In this group were those patients having nerve damage, chronic tetany, severe hypertension, and other sequelae.

TABLE 5. POSTOPERATIVE REHABILITATION

Result	Number of patients	Percentage
Euthyroid	225	87.9
Good	19	7.4
Unsatisfactory*	12	4.7
	256	100.0

* Severe hypertension, chronic tetany, nerve injury, auricular fibrillation.

TABLE 6. MORTALITY RATE

Period	Number of deaths	Incidence
1935–49	6	2.1%
1939–49	4	1.8%
1944–49	0	0

Mortality

There have been 6 deaths, resulting in a mortality rate of 2.1 per cent as indicated in Table 6. There have been no deaths since September 6, 1944. This we attribute to the advent of the newer antithyroid drugs and to improved operative technique.

Although the mortality rate is higher than we desire, it is to be remembered that this operation has especially been stressed as the procedure of

choice in certain great-risk groups. These are 1) extremely toxic patients whom we regard most likely to have a recurrence; 2) patients having recurrent hyperthyroidism; and 3) patients presenting severe complications, especially cardiac, in whom we believe it is particularly important to avoid persistent hyperthyroidism and in whom further operation would be especially undesirable or impossible.

CONCLUSIONS

1. Subtotal thyroidectomy leaves remnants of thyroid tissue which may continue to secrete an abnormal product and cause persistent manifestations of hyperthyroidism requiring further antithyroid treatment in as many as 17.5 per cent of patients with diffuse toxic goiter. Therefore, we conclude that the operation is not an entirely satisfactory method of treatment of diffuse toxic goiter.

2. There exists no available therapeutic agent capable of restoring the abnormal thyroid gland to a normal cytologic state and of so maintaining it. Furthermore, medical treatment is associated with an even higher recurrence rate than is subtotal thyroidectomy.

3. Total ablation of all abnormal thyroid secretion affords permanent relief from hyperthyroidism. This can be accomplished by total thyroidectomy and we believe it constitutes a rational method of surgical treatment. Our experience indicates that the operation can be performed with a morbidity and a mortality rate comparing favorably with those attending the technically less difficult subtotal procedure. We are certain that the rehabilitation is superior and that the undesirable and dangerous complications secondary to a persistent abnormal thyroid secretion are abolished.

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TREATMENT OF POSTOPERATIVE HYPERTHYROIDISM WITH ANTITHYROID DRUGS*

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IT is generally accepted that the antithyroid drugs are useful in postoperative hyperthyroidism but no extended study has been made to determine their comparative position in relation to the older methods of treatment. Are they more useful than iodine or x-ray irradiation? Is their action more enduring? Can they be administered safely over extended periods? Do they produce reduction in thyroid enlargement and exophthalmos? And, finally, do they offer promise of eliminating difficult secondary surgery?

CLINICAL MATERIAL

Twenty-eight patients with postoperative hyperthyroidism, in most of whom the disease had been uncontrolled by other methods, were treated with either thiouracil or propylthiouracil or both, and form the basis of this report. Eighteen had persistent hyperthyroidism, their symptoms having failed to disappear within thirty days after operation. Nine had recurrences, classed as such because following operation they had passed through a period of freedom from symptoms without aid from medication. One had recurrence after each of two operations and persistence after a third unsuccessful operation. All but one of the patients with persistent symptoms had had subtotal thyroidectomy for toxic diffuse goiter. Of those with recurrences, 7 had been operated upon for toxic diffuse goiter and 2 for toxic adenoma. The low incidence of residua in those with toxic adenoma has been noted generally, as has the predominance of persistence and recurrence following operations for toxic diffuse goiter.

In evaluating the effectiveness of treatment for either form of postoperative thyrotoxicosis it is important to separate, whenever possible, the subjective from the objective signs, determining the portion of the symptom-complex attributable to the thyrotoxicosis and that caused by nervous instability. This is especially essential in the patients operated upon for toxic diffuse goiter, since many of these present an array of con-

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fusing nonspecific signs, as emphasized recently by Martin (1). Accordingly, as much of the significant data as was available before and after operation and subsequent to treatment for residual disturbances, was so classified. The size of the gland, the basal metabolic rate, weight loss, eye signs, tachycardia and tremor were placed on the objective side, whereas nervousness, exertional dyspnea, sweating or heat intolerance, lassitude, headache, insomnia, phobias, chest pain and diarrhea were classed as subjective. Aggravating factors such as infections, psychic trauma, pregnancy and the menopause were given due consideration. The results of treatment, other than with the thioureas, were also taken into account.

Group 1

The first group of 6 patients (Table 1) presented neither thyroid enlargement nor elevated basal metabolic rate. All were females whose average age was 43 years. One had had ligation of the upper poles with subtotal resection nine years later; 1 had developed postoperative cord paralysis; and 1, a progressive exophthalmos following two thyroidectomies. Only 1 of the group (patient 5) had not been severely toxic previous to operation. The symptoms were persistent in 5 and recurrent in 1. There were no aggravating factors in 2, psychic trauma was of significance in 2 and menopausal disturbance was prominent in the remaining 2.

Treatment with iodine in nearly all, and x-ray irradiation in 2 had been of little avail. Some were being treated with thiouracil, some with propylthiouracil and some with both, in ordinarily adequate amounts for periods ranging from four to seventeen months. The BMR was uninfluenced, as were most of the symptoms.

Results were uniformly poor and it is readily observed that this type of patient, suffering from long-standing nervous instability with very little if any thyrotoxicosis, is unresponsive to any form of therapy aimed solely at this latter condition. It is useful, however, to institute a course of treatment because of its beneficial effect on any true thyrotoxic residua that may be present.

Group 2

In the second group of 19 patients (Table 2), more decisive evidence of residual thyrotoxicosis was found. Here among 14 females and 5 males with an average age of 42 years, were 7 with recurrences developing from one to twenty-five years after operation. Four had had two operations and 1, four operations. Thyroid enlargement of varying degree was present in 13 and absent in 6. All showed elevation of the BMR, the average being plus 29 per cent for the recurrent, and plus 28 per cent for the persistent cases. In 8, no aggravating factors could be ascertained. The menopause

TABLE 1

Patient	Age	Sex	Type of goiter and date of operation	Symptoms* ("S") after operation; persistent or recurrent	Aggravating factors†	Previous treatment and results	Presenting signs at beginning of antithyroid drug therapy	Antithyroid drug therapy	Results
1. R.D.J.	46	F	Toxic diffuse 1926—Ligation 1935—Subtotal thyroidectomy	Diffuse enlargement. Persistent until thyroidectomy. *Persistent.* "S": 2, 4, 5, 6, 7, 8, 11.	None	Lugol's solution for 9 years. No improvement.	BMR plus 2%; no palpable thyroid; no weight change; cholesterol, 217 mg.%. "S": 2, 4, 5, 6, 7, 8, 11; secondary anemia.	Thiouracil 0.3 Gm. daily for 4½ months; iron for secondary anemia.	BMR minus 4%; thyroid not palpable; no weight change; anemia improved; "S": 4, 5, 6, 7, 11.
2. M.B.	44	F	Toxic diffuse 1929—Subtotal thyroidectomy followed by cord paralysis	No palpable thyroid; BMR not known. *Persistent.* "S": 1a, 2, 3, 4, 6.	None	Lugol's solution intermittently for 16 years. No improvement.	BMR minus 14%; no palpable thyroid; no weight change; "S": 1a, 2, 3, 4, 6.	Thiouracil 0.2 Gm. daily for 10 months; propylthiouracil 0.050 Gm. daily for 4 months.	BMR minus 9%; thyroid not palpable; no weight change; "S": 1a, 2, 3, 4, 6.
3. M.Ba.	38	F	Toxic diffuse 1928—Subtotal thyroidectomy	No palpable thyroid; BMR not known. *Persistent.* "S": 1a, 2, 4, 9, 10, 11.	Menopause	Lugol's solution intermittently for 17 years.	BMR minus 6%; no palpable thyroid; no weight change; "S": 1a, 2, 4, 9, 10, 11.	Propylthiouracil 0.150 Gm. daily for 18 months.	BMR minus 3%; no palpable thyroid; no weight change; "S": 1a, 2, 4, 9, 10, 11.
4. I.K.	43	F	Toxic diffuse 1934—Subtotal thyroidectomy 1937—Subtotal thyroidectomy	*Persistent.* "S": 1, 1a, 2, 4, 6, 8. BMR minus 13%; no palpable thyroid; no weight change; progressive exophthalmos; "S": 1, 1a, 2, 4, 6, 8.	Menopause	Lugol's solution; x-ray therapy, and bilateral tarsorrhaphy.	BMR minus 25%; no palpable thyroid; no weight change; marked exophthalmos; "S": 1, 1a, 2, 4, 6, 8.	Thyroid substance and stilbestrol. No antithyroid drug given because of progressive exophthalmos.	BMR minus 2%; no palpable thyroid; no weight change; "S": 1, 1a, 2, 4, 6, 8.
5. H.C.	36	F	Toxic diffuse 1942—Subtotal thyroidectomy	BMR plus 5%; slight thyroid enlargement; no weight change. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 7, 8, 9, 10, 12.	Psychic trauma	Lugol's solution and x-ray therapy to pituitary.	BMR minus 5%; no palpable thyroid; no weight change; "S": 1, 1a, 2, 3, 4, 6, 7, 8, 9, 10, 12.	Thiouracil 0.4 Gm. daily for 15 months.	BMR minus 1%; no palpable thyroid; weight loss 3 Kg.; "S": 1, 1a, 2, 3, 4, 6, 7, 8, 9, 10, 12.
6. C.M.	50	F	Toxic diffuse 1928—Subtotal thyroidectomy	BMR not known. No palpable thyroid. 1942: pernicious anemia; diabetes mellitus. *Recurrent* hyperthyroidism; "S": 1a, 2, 3, 4, 6, 9, 12.	Psychic trauma	Treatment with liver extract, diet, insulin.	BMR minus 5%; no palpable thyroid; weight loss; "S": 1a, 2, 3, 4, 6, 9, 12.	Thiouracil 0.3 Gm. daily for 14 months; propylthiouracil 0.100 Gm. daily for 3 months. No antithyroid drugs for 18 months.	BMR plus 32 and 22%; no palpable thyroid; weight loss 18 Kg.; anemia improved; diabetes poorly controlled; "S": 1a, 2, 3, 4, 6, 9, 12.

* Symptoms ("S") include: *1.* Exophthalmos; *1a.* Lid-lag; *2.* Palpitation; *3.* Tremor; *4.* Nervousness; *5.* Exertional dyspnea; *6.* Sweating or heat intolerance; *7.* Lassitude; *8.* Headache; *9.* Insomnia *10.* Phobias; *11.* Chest pain; *12.* Diarrhea.

† Aggravating factors include: Intercurrent infection, psychic trauma, pregnancy, menopause.

was a factor in 4, dental infection in 2, psychic trauma in 2, and pregnancy, leg amputation for gangrene, and a ruptured appendix were factors in separate cases.

Lugol's solution had been used for varying periods in all but 4 patients (Nos. 9, 20, 24, 25) and x-ray therapy had been given in addition to two others (Nos. 10 and 15). In no instance had there been satisfactory control of either the objective or subjective symptoms.

Treatment with thiouracil or propylthiouracl was given to all patients. The dosage averaged 0.4 Gm. of the former daily for 9.2 months and 0.130 Gm. of the latter daily for 18.4 months. Drug fever developed in 1 patient (No. 8) after six weeks of propylthiouracil, and Lugol's solution was substituted, even though it had not been previously effective. In a second patient (No. 14) with an enormously enlarged gland, satisfactory control (but without significant reduction in gland size) was achieved only after the combined use of 0.300 Gm. of propylthiouracil and 30 minims of Lugol's solution daily for seven months and the extraction of a number of abscessed teeth. Only then did the symptoms subside sufficiently to permit performance of the fourth thyroidectomy.

Those patients in whom the menopause was an aggravating factor (Nos. 7, 8, 11 and 22) were helped by estrogenic therapy and one of the patients with psychic trauma (No. 21) was aided by psychotherapy.

The response to treatment was generally gratifying. The average final BMR was minus 12 per cent in both persistent and recurrent cases. In 7 of the 13 with thyroid enlargement (Nos. 7, 11, 13, 15, 19, 21, 22) the gland was no longer palpable after an average period of treatment of twenty-four months. The patient who developed drug fever (No. 8) and was treated with Lugol's solution for the following twenty-one months also showed disappearance of the thyroid enlargement. One patient (No. 14) had thyroidectomy and the remaining 4 (Nos. 9, 23, 24, 25) showed significant reduction in thyroid size after nine, ten, fifteen and twenty-nine months of treatment respectively.

Five patients (Nos. 8, 9, 13, 21, 22) are still under treatment; one patient (No. 17) died; one (No. 14) has had thyroidectomy recently, but the remaining 12 have had no antithyroid therapy for an average of thirteen months. All but 3 patients (Nos. 8, 17, 23) gained weight.

The entire group showed improvement in most of the symptoms but some degree of exophthalmos, or lid lag, or both, remained in every patient.

This second group of patients with either persistent or recurrent toxic diffuse goiter, showed reduction in the BMR, decrease in or disappearance of thyroid enlargement, gain in weight and alleviation of disturbing symptoms with only lid lag and/or exophthalmos persisting in all to some degree.

TABLE 2

Patient	Age	Sex	Type of goiter and date of operation	Symptoms* ("S") after operation; persistent or recurrent	Aggravating factors†	Previous treatment and results	Presenting signs at beginning of antithyroid drug therapy	Antithyroid drug therapy	Results
7. B.K.	52	F	Toxic diffuse 1940—Subtotal thyroidectomy	BMR not known; no weight loss. *Recurrent* after 5 years. "S": 1, 1a, 2, 3, 4, 6, 9, 10.	Menopause	Lugol's solution for 2 months without improvement.	BMR plus 3%; weight loss 9 Kg.; thyroid bilaterally enlarged; "S": 1, 1a, 2, 3, 4, 6, 9, 10.	Thiouracil 0.4 Gm. daily for 1 month; propylthiouracil 0.150 Gm. daily for 16 months; estrogens; no treatment for 12 months.	BMR minus 9%; weight gain 6 Kg.; thyroid not palpable; "S": 1, 1a, 4, 9, 10. —
8. Z.B.	49	F	Toxic diffuse 1922—Subtotal thyroidectomy	BMR not known; no weight loss; bilateral thyroid enlargement. *Recurrent* after 19 years; "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9, 10.	Menopause	Lugol's solution for 1 year with good control; no control since.	BMR plus 5%; no palpable thyroid; no weight loss; "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9, 10.	Propylthiouracil 0.100 Gm. daily for 6 weeks *followed by drug fever;* Lugol's solution for 21 months; estrogenic therapy; still under treatment.	BMR minus 18%; weight loss 2 Kg.; thyroid not palpable; "S": 1, 1a, 4, 8, 9, 10.
9. T.B.	36	F	Toxic diffuse 1939—Subtotal thyroidectomy	BMR not known; weight loss 5 Kg.; bilateral thyroid enlargement. *Recurrent* after 9 years. "S": 1, 1a, 2, 3, 4, 6, 9.	Pregnancy	None	BMR plus 57%; weight loss 5 Kg.; bilateral thyroid enlargement—R>L; "S": 1a, 2, 3, 4, 6, 9.	Propylthiouracil 0.200 Gm. daily for 9 months; still under treatment.	BMR minus 11%; weight gain 3 Kg.; thyroid smaller; "S": 1a.
10. B.L.	31	F	Toxic diffuse 1938—Hemithyroidectomy 1938—Hemithyroidectomy 1941—Subtotal-thyroidectomy	BMR not known; weight loss not known; no palpable thyroid. *Persistent.* "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9.	None	Lugol's solution without relief; 10 x-ray treatments Feb.–Oct. 1944.	BMR plus 23%; thyroid not palpable; no weight change; "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9.	Thiouracil 0.3 Gm. daily for 9 months; propylthiouracil 0.150 Gm. daily for 16 months. No treatment for 16 months.	BMR minus 16%; weight gain 3 Kg.; thyroid not palpable; "S": 1, 1a.
11. J.B.	48	F	Toxic diffuse 1943—Subtotal thyroidectomy	BMR plus 35% before operation; BMR plus 52% after operation; weight loss not known; bilateral thyroid enlargement; progressive exophthalmos. *Persistent.* "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9, 10.	Menopause	Lugol's solution without relief; (iodide rash).	BMR plus 25%; Rt. lobe enlarged; weight loss unknown; "S": 1, 1a, 2, 3, 4, 5, 6, 8, 9, 10.	Thiouracil 0.4 Gm. daily for 3 months; propylthiouracil 0.200 Gm. daily for 19 months; estrogens; no medication for 8 months.	BMR minus 2%; weight gain 9 Kg.; thyroid not palpable; "S": 1, 1a.
12. C.J.	29	F	Toxic diffuse 1943—Subtotal thyroidectomy 1944—Subtotal thyroidectomy	BMR not known; weight loss unknown. *Persistent.* "S": 1a, 2, 3, 4, 6, 8, 9.	None	Lugol's solution without relief.	BMR plus 30%; no palpable thyroid; weight loss unknown; "S": 1a, 2, 3, 4, 6, 8, 9.	Thiouracil 0.6 Gm. daily for 4 months; no treatment for 2 years.	BMR minus 10%; weight gain 1 Kg.; thyroid not palpable; "S": 1a.

* and †: *See* corresponding footnotes to Table 1

TABLE 2—(*Continued*)

Patient	Age	Sex	Type of goiter and date of operation	Symptoms* ("S") after operation; persistent or recurrent	Aggravating factors†	Previous treatment and results	Presenting signs at beginning of antithyroid drug therapy	Antithyroid drug therapy	Results
13. J.R.F.	40	M	Toxic diffuse 1940—Subtotal thyroidectomy	BMR plus 70% before operation; weight loss unknown; bilateral thyroid enlargement. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 8, 9.	None	Lugol's solution for 1 year without relief.	BMR plus 25%; weight loss unknown; thyroid enlargement at isthmus; "S": 1, 1a, 2, 3, 4, 6, 8, 9.	Thiouracil 0.4 Gm. daily for 17 months; propylthiouracil 0.150 Gm. daily for 3.5 months; still under treatment.	BMR minus 20%; weight gain 7 Kg.; no palpable thyroid; "S": 1, 1a.
14. H.L.	51	M	Toxic diffuse 1921—Subtotal thyroidectomy 1946—Subtotal thyroidectomy 1948—Unsuccessful thyroidectomy 1948—Subtotal thyroidectomy	*Recurrent* after 25 years. *Recurrent* after 1 year; BMR unknown; weight loss 19 Kg.; bilateral thyroid enlargement; "S": 1, 1a, 2, 3, 4, 5, 6, 9.	Abscessed teeth	Lugol's solution failed to stop progression of symptoms after second and third thyroidectomies.	BMR plus 75%; thyroid enormously enlarged; weight loss unknown; "S": 1, 1a, 2, 3, 4, 5, 6, 9.	Propylthiouracil 0.300 Gm. daily for 8 months with Lugol's—30 minims daily—for 7 months; extraction of infected teeth.	BMR minus 12%; weight gain 5 Kg.; subtotal thyroidectomy followed by cord paralysis; "S": 1a.
15. P.H.	16	F	Toxic diffuse 1945—Subtotal thyroidectomy	BMR plus 54% before operation; weight loss unknown; thyroid slightly enlarged. *Persistent.* "S": 1, 1a, 2, 3, 4, 5, 8.	None	Lugol's solution for 12 months without relief; x-ray therapy for for 3 months.	BMR plus 22%; weight loss 3 Kg.; bilateral thyroid enlargement; "S": 1, 1a, 2, 3, 4, 5, 8.	Thiouracil 0.2 Gm. daily for 2 months; propylthiouracil 0.050 Gm. daily for 24 months; no treatment for 9 months.	BMR minus 15%; weight gain 3.5 Kg.; no palpable thyroid; "S": 1a.
16. R.K.	48	M	Toxic diffuse 1933—Subtotal thyroidectomy 1939—Subtotal thyroidectomy	BMR plus 47% 2 years after first operation; thyroid enlarged; weight stationary; diabetes mellitus. *Recurrent.* "S": 1, 1a, 2, 3, 4, 6, 9.	None	Lugol's solution relieved for 8 years then ineffective.	BMR plus 28%; weight stationary; no palpable thyroid; diabetes difficult to control; "S": 1, 1a, 2, 3, 4, 6, 9.	Thiouracil 0.4 Gm. daily for 15 months; propylthiouracil 0.1 Gm. daily for 32 months; no treatment for 4 months.	BMR minus 10%; no palpable thyroid; weight gain 2.5 Kg.; diabetes still not well controlled; "S": 1a.
17. M.D.	68	F	Toxic diffuse 1915—Pole ligation 1935—2-stage thyroidectomy 1940—Radium therapy	BMR unknown; weight loss unknown; no palpable thyroid. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 9, 10, 12.	None	Lugol's solution almost continuously without relief.	BMR plus 27%; weight loss marked; no palpable thyroid; "S": 1, 1a, 2, 3, 4, 6, 9, 10, 12.	Thiouracil 0.2 Gm. daily for 29 weeks.	BMR minus 7%; no palpable thyroid; weight gain 5.5 Kg.; "S": 1a, 4, 9. (Developed dementia, was institutionalised and died.)
18. L.D.	75	M	Toxic diffuse 1926—Subtotal thyroidectomy	Weight loss unknown: no palpable thyroid; BMR plus 63% 3 years after operation. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 9.	Abscessed teeth	Lugol's solution for 3 years without relief, then intermittently.	BMR plus 51%; weight loss 7 Kg.; thyroid not palpable; "S": 1, 1a, 2, 3, 4, 5, 6, 9.	Thiouracil 0.6 Gm. daily for 6 months. No treatment for 5 months.	BMR minus 10%; gained 5.5 Kg.; no palpable thyroid; "S": 1, 1a. (Developed carcinoma of cecum and died following surgery.)

TABLE 2—(*Continued*)

Patient	Age	Sex	Type of goiter and date of operation	Symptoms* ("S") after operation; persistent or recurrent	Aggravating factors†	Previous treatment and results	Presenting signs at beginning of antithyroid drug therapy	Antithyroid drug therapy	Results
19. G.D.	31	F	Toxic diffuse 1943—Subtotal thyroidectomy	BMR plus 48% before operation; no palpable thyroid; no weight change. *Persistent.* "S": 1a, 2, 3, 4, 6, 8, 9.	None	Lugol's solution for 6 months without relief.	BMR plus 27%; bilateral thyroid enlargement; no weight change; "S": 1a, 2, 3, 4, 6, 8, 9.	Thiouracil 0.8 Gm. daily for 4 months. No treatment for 8 months.	BMR minus 2%; no palpable thyroid; weight gain 1 Kg.; "S": 1a.
20. C.S.	36	F	Toxic diffuse 1926—Subtotal thyroidectomy	BMR unknown; no palpable thyroid; weight loss unknown. *Recurrent* after 19 years. "S": 1, 1a, 2, 3, 4, 6, 8, 9.	Ruptured appendix with generalized peritonitis.	Developed symptoms after recovery from peritonitis.	BMR plus 23%; no palpable thyroid; weight loss unknown; "S": 1a, 2, 3, 4, 6, 9.	Thiouracil 0.4 Gm. daily for 1 year; no treatment for 8 months.	BMR minus 4%; no palpable thyroid; weight gain 22 Kg.; "S": 1a.
21. H.P.	35	F	Toxic diffuse 1940—2-stage subtotal thyroidectomy	BMR unknown; weight loss unknown; thyroid enlarged again soon after operation. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 8, 9, 10.	Psychic trauma	Lugol's solution without relief.	BMR plus 24%; weight loss unknown; thyroid enlargement; Rt. lobe and isthmus; "S": 1, 1a, 2, 3, 4, 6, 8, 9, 10.	Propylthiouracil 0.100 Gm. daily for 30 months; psychotherapy for 14 months; still under both forms of treatment.	BMR minus 25%; weight gain 4.5 Kg.; no palpable thyroid; "S": 1, 1a.
22. E.S.	40	F	Toxic diffuse 1942—Subtotal thyroidectomy	BMR plus 54% before operation; weight stationary; thyroid not palpable. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 8, 9.	Menopause	Lugol's solution without relief.	BMR plus 11%; bilateral thyroid enlargement; weight loss unknown; "S": 1, 1a, 2, 3, 4, 6, 8, 9.	Propylthiouracil 0.150 Gm. daily for 23 months; estrogens; still under treatment.	BMR minus 11%; no palpable thyroid; weight gain 3 Kg.; "S": 1, 1a, 6, 8.
23. J.M.	42	M	Toxic diffuse 1929—Subtotal thyroidectomy	BMR unknown; no weight change; thyroid not palpable. *Persistent.* "S": 1, 1a, 2, 3, 4, 6, 8. Frequent urticaria.	None	Lugol's solution intolerable because of iodide rash.	BMR plus 30%; palpable rt. lobe and isthmus; weight stationary; "S": 1, 1a, 2, 3, 4, 6.	Thiouracil 0.4 Gm. daily for 9 months; propylthiouracil 0.05 Gm. daily for 1 month; no treatment for 24 months.	BMR minus 5% no weight change; thyroid barely palpable; "S": 1, 1a, 6.
24. M.M.	64	F	Toxic diffuse 1923—Subtotal thyroidectomy	BMR unknown; weight loss unknown; thyroid not enlarged. *Recurrent* after 23 years. "S": 1a, 2, 3, 4, 6, 12.	Amputation of rt. leg for diabetic gangrene.	Diabetes difficult to control with diet and insulin.	BMR plus 14%; palpable substernal bilateral thyroid enlargement; weight loss unknown; diabetes hard to control; "S": 1a, 2, 3, 4, 6, 12.	Propylthiouracil 0.150 Gm. daily for 15 months; no treatment for 16 months.	BMR minus 8%; weight gain 3 Kg.; thyroid barely palpable; diabetes easily controlled; "S": 1a.
25. F.M.	39	F	Toxic diffuse 1926—Subtotal thyroidectomy	BMR unknown; weight loss unknown. *Persistent.* Thyroid enlarged. "S": 1, 1a, 2, 3, 4, 6, 9.	Psychic trauma (husband in military service.)	Sedatives, with temporary improvement.	BMR plus 44%; bilateral thyroid enlargement; weight loss 19 lbs.; cholesterol 250 mg.%; "S": 1, 1a, 2, 3, 4, 6, 9.	Thiouracil 0.4 Gm. daily for 9 months; then 0.2 Gm. daily for 3 months; then 0.1 Gm. daily for 12 months; propylthiouracil 0.100 Gm. daily for 15 months; no medication for 21 months.	BMR minus 18%; weight gain 9 Kg.; thyroid barely palpable; "S": 1a.

Group 3

In the third group of 3 patients (Table 3) the average age was 64. Two were females and one was a male, and the symptom-free interval since operation was eleven and ten years respectively in the 2 recurrent cases (Nos. 26 and 27). The patient with persistence (No. 28) had poorly controlled diabetes and hypertension, there was no palpable thyroid tissue and there had been poor response to Lugol's solution administered for a period of three years. The initial BMR was plus 14 per cent and after treatment with 0.150 Gm. of propylthiouracil daily for nine months, no evidence of improvement was noted.

Marked improvement occurred, however, in the 2 patients with recurrence. In the man with hypertension (No. 26) both right and left-sided cardiac failure had developed, which failed to respond to therapy. The response to treatment with 0.150 Gm. of propylthiouracil daily was striking, compensation being restored after four weeks. This medication was continued for a total of nine months and was then stopped. Death from cerebral thrombosis occurred suddenly one year later. Patient No. 27 had had no relief from Lugol's solution administered for three years. There was a nodule in the region of the right lobe of the thyroid and the BMR was plus 50 per cent. Nine months' treatment with 0.200 Gm. of propylthiouracil daily resulted in a weight gain of 8 Kg., reduction of the BMR to minus 8 per cent and alleviation of all symptoms except the lid-lag. The symptoms recurred after thirteen months without treatment and, as before, improvement followed four months of therapy with 0.200 Gm. of propylthiouracil daily.

Thus, in this small group, in the one patient with the full blown picture of thyrotoxicosis, improvement followed treatment with propylthiouracil without, however, any change in the thyroid nodule. Improvement also occurred in the patient in whom cardiac decompensation was apparently aggravated by a residual thyrotoxicosis. In the third patient no beneficial effect was observed.

DISCUSSION

Postoperative thyrotoxicosis, whether persistent or recurrent, has always presented a difficult problem. Opinion as to its appropriate treatment has ranged from unbending adherence to surgery to temperate efforts at medical management with reoperation only as a final recourse. Thompson and Preston (2) have shown that in some patients with persistent thyrotoxicosis (following operation for toxic diffuse goiter) spontaneous remission, even accompanied by a decrease in palpable gland, could follow in from three months to four years after operation. This alone should encourage temporizing. Some residua are undoubtedly due to inadequate

TABLE 3

Patient	Age	Sex	Type of goiter and date of operation	Symptoms* ("S") after operation; persistent or recurrent	Aggravating factors†	Previous treatment and results	Presenting signs at beginning of antithyroid drug therapy	Antithyroid drug therapy	Results
26. H.H.	67	M	Toxic adenoma 1936—Subtotal thyroidectomy	BMR not known; no palpable thyroid; no weight loss. *Recurrent* after 11 years.	Hypertensive heart disease with uncontrolled decompensation.	No improvement after bed rest, digitalis, diuretics and salt poor diet.	BMR plus 14%; no palpable thyroid; weight gain (edema); "S": 1a, 3.	Propylthiouracil 0.150 Gm. daily for 9 months; no treatment for 11 months.	No palpable thyroid; weight loss (edema); compensation restored; "S": 1a. Died of cerebral thrombosis 12 months later.
27. E.N.	72	F	Toxic adenoma 1932—Subtotal thyroidectomy	BMR not known; palpable nodule. *Recurrent* after 10 years.	None	Lugol's solution for 3 years with no improvement.	BMR plus 50%; nodule in rt. lobe; weight loss 6 Kg.; "S": 1, 1a, 2, 3, 4, 6, 9, 11.	Propylthiouracil 0.200 Gm. daily for 9 months; no treatment for 13 months. *Recurrence.* Propylthiouracil 0.200 Gm. daily for 4 months.	BMR minus 8%; weight gain 8 Kg.; palpable nodule; "S": 1a. BMR minus 5%; weight gain 6 Kg.; palpable nodule; "S": 1a.
28. E.R.	54	F	Toxic adenoma 1943—Thyroidectomy	BMR not known; no palpable thyroid; weight loss 3.5 Kg. Diabetes developed 2 months postoperatively. *Persistent.* "S": 1a, 2, 4, 8.	Hypertension and diabetes.	Lugol's solution; diet and insulin.	BMR plus 14%; no palpable thyroid; weight loss 3.5 Kg.; "S": 1a, 2, 4, 8.	Propylthiouracil 0.150 Gm. daily for 10 months.	BMR plus 10%; no weight change; no palpable thyroid; "S": 1a, 2, 4, 8.

surgery, but Pemberton (3) maintains that there is no logical basis for assuming that the most common cause of recurrence of toxic diffuse goiter after conservative subtotal thyroidectomy is incompleteness of the operation. There may be a recurrence of the stimulus that caused the disease originally. The teaching of Richter (4) advocating almost total thyroidectomy as a routine procedure, with feeding of thyroid afterward, is not generally approved or followed. It appears better to have a few cases of residual hyperthyroidism than to have many cases of hypothyroidism (5). According to Gillette (6), total thyroidectomy results in too much morbidity with risk of section of laryngeal nerves.

A degree of persistence in many of those patients operated on for toxic diffuse goiter has been recognized as unavoidable because of the continued emotional stimuli and the added psychic trauma of the surgical procedure. For these patients, the treatment formerly followed was to administer iodine for six months or longer after thyroidectomy, eradicate focal infections, reduce strain and worry, improve occupational factors, eliminate coffee and tobacco and promote weight gain with careful supervision for a two-year postoperative period (7, 8).

The more recent view, shared by many, (9) is that the treatment of recurrences is the special sphere of the antithyroid substances or of radioactive iodine. This does not exclude surgical treatment. The validity of this view is supported by the present experience with 28 patients in whom adequate control of residual thyrotoxicosis was effected with antithyroid drugs in 21, after other forms of therapy had failed. As with previous forms of medical therapy, the best results followed prolonged therapy, confirming the long noted observation that these patients do best when kept under surveillance for at least two years after operation.

SUMMARY

1. Six patients out of a group of 28 with postoperative thyrotoxicosis, who showed neither thyroid enlargement nor elevated basal metabolism and were unresponsive to other treatment, were suffering mainly from nervous instability and showed no improvement with antithyroid therapy.

2. Eighteen patients previously operated upon for toxic diffuse goiter and showing more decisive evidence of residual thyrotoxicosis, responded to antithyroid therapy with reduction in basal metabolic rate, diminution in size of the thyroid enlargement when present, gain in weight and relief of most of the symptoms, with the exception of lid lag and exophthalmos. Five of this group are still under treatment but 12 have remained in remission for an average of thirteen months without any treatment. One male patient who had had two recurrences after separate operations and persistence after a third operation, presented an enormous gland and

marked thyrotoxicosis which was controlled only after combined treatment with propylthiouracil and iodine and removal of numerous infected teeth. Thyroidectomy was successfully performed and although there has been no recurrence in the three months that have elapsed, vocal cord paralysis has developed.

3. In one of 3 patients previously operated upon for toxic adenoma and showing signs of persistence complicated by diabetes and hypertension, the thyrotoxicosis was not controlled by treatment with propylthiouracil. Both of the others responded very well but the nodule present in one remained unchanged.

CONCLUSIONS

From the results observed in a group of 28 patients with postoperative thyrotoxicosis, the antithyroid drugs (propylthiouracil and thiouracil) were of definite value in controlling the disease, lending themselves to prolonged use without complications. Furthermore, the response to their use in the troublesome borderline group of patients with predominant symptoms of nervous instability was extremely helpful in deciding whether true hyperthyroidism was still a part of the picture. From this experience, therefore, it would seem advantageous for every patient with postoperative hyperthyroidism to have a course of antithyroid therapy before deciding on other types of treatment.

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The Association for the Study of Internal Secretions Request for Biographical Data for New Roster

The membership roll of the Association is being revised in preparation for the issuance of a new Roster as of December 31, 1949. *Copy for this must be in the hands of the printer not later than October 1, 1949.*

Return postal cards are being mailed to members requesting the following information:

Name.....Degrees.....

Mailing Address.....

.....

Teaching or Research Position:.....

.....

.....

If in active practice of medicine, specialty:.....

.....

Members are urged to complete and return the card immediately and to keep the Secretary informed at all times of any change in the above.

HENRY H. TURNER, M.D.
Secretary-Treasurer
1200 North Walker Street
Oklahoma City 3, Oklahoma

The 1950 Meeting of the Association for the Study of Internal Secretions

The next Annual Meeting of the Association will be held in San Francisco, June 23 and 24, 1950. The hotel in which we shall meet has not yet been determined because of the uncertainty of AMA commitments, but it will be announced in an early issue of the Journal. Members are urged to make their hotel reservations as soon as possible.

The 1950 Awards of the Association for the Study of Internal Secretions

FELLOWSHIPS

The Ayerst, McKenna and Harrison Fellowship

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949.

The Schering Fellowship in Endocrinology

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Lawrence Wilson.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $2,500, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

AWARDS

The E. R. Squibb and Sons Award

The E. R. Squibb & Sons Award of $1,000 was established in 1939, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. E. A. Doisy; in 1945

to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; and in 1949 to Dr. Herbert M. Evans. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

The Ciba Award

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; and in 1949 to Dr. George Sayers. The Award is for $1,200. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.

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NOMINATIONS

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on *special application forms* which may be obtained from the *Secretary*, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, and returned to him not later than *March 15, 1950.*

The 1950 Meeting of the American Goiter Association

The next meeting of the American Goiter Association will be held at the Hotel Shamrock, Houston, Texas, March 9, 10, and 11, 1950. It is recommended that all physicians wishing to attend make their hotel reservations early.

Award of the American Goiter Association

VAN METER PRIZE

THE AMERICAN GOITER ASSOCIATION again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9, 10 and 11, 1950, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy *in duplicate* should be sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East St. Vrain Street, Colorado Springs, Colorado, not later than *January 15, 1950.* The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.